7.1.1 Deaths

There were no deaths in NEB-122.

7.1.2 Other Serious Adverse Events

No serious adverse events occurred.

7.1.3 Dropouts and Other Significant Adverse Events

Sixteen patients withdrew from the study, including 1 subject receiving nebivolol, 9 subjects receiving atenolol, 3 subjects receiving moxifloxacin, and 3 subjects receiving placebo.

7.1.3.1 Overall profile of dropouts (from Case Report Forms) (NEB-122)

Subject	Treatment	Age	Ethnicity	Gender	Metabolism	Date of Randomization	Date of Discontinuation	Symptoms	Reason for Withdrawal
	Placebo	41	Caucasian	Male	Extensive	6/8/2003	6/20/2003	Dizziness 6/19/2003	Withdrew Consent--NRS
	Placebo	41	Hispanic	Female	Extensive	7/10/2003	7/10/2003	-	Withdrew Consent--NRS; Inclusion waiver granted, but no waiver found in records
	Placebo	28	Black	Female	Extensive	7/21/2003	7/28/2003	Headache, fever to 101°F, diarrhea 7/26/2003	Patient discontinued due to Adverse Event
	Nebivolol	27	Black	Male	Extensive	6/18/2003	6/22/2003	-	Withdrew Consent--NRS
	Atenolol	49	Caucasian	Male	Extensive	6/18/2003	6/20/2003	-	"Flashcard not able to record data"
	Atenolol	25	Hispanic	Female	Extensive	6/18/2003	6/22/2003	-	Withdrew Consent--NRS
	Atenolol	29	Caucasian	Male	Extensive	6/27/03	7/1/2003	-	Withdrew Consent--NRS
	Atenolol	36	Caucasian	Male	Extensive	6/27/2003	7/1/2003	-	Withdrew Consent--NRS
	Atenolol	43	Caucasian	Female	Extensive	6/27/2003	6/29/2003	Developed toothache 6/28/2003, still ongoing	Patient discontinued due to Adverse Event
	Atenolol	55	Caucasian	Female	Extensive	7/10/2003	7/11/2003	No AE recorded	Patient discontinued due to Adverse Event
	Atenolol	37	Hispanic	Male	Extensive	7/10/2003	7/12/2003	-	Withdrew Consent--NRS

	Atenolol	26	Caucasian	Female	Extensive	7/10/2003	7/12/2003	-	Withdrew Consent--NRS
	Atenolol	40	Hispanic	Male	Extensive	Not recorded	7/25/2003	-	Withdrew Consent--NRS
	Moxifloxacin	43	Caucasian	Male	Extensive	6/18/2003	6/24/2003	-	Withdrew Consent--NRS
	Moxifloxacin	53	Caucasian	Male	Extensive	7/10/2003	7/11/2003	-	Investigator withdrew patient due to elevated blood pressure (148/100)
	Moxifloxacin	37	Hispanic	Female	Extensive	7/10/2003	7/11/2003	-	Investigator withdrew patient due to elevated blood pressure (128/98, 136/94)

NRS: No reason specified
(Compiled by Hicks K from Case Report Forms)

Only one patient receiving nebivolol discontinued the study. Of the 16 subjects who discontinued the study, 10 patients withdrew consent without specifying a particular reason, and 3 patients withdrew due to adverse events, with one of these adverse events being "unspecified." Additionally, 2 patients were withdrawn by the investigator due to elevated blood pressure on Moxifloxacin, and 1 patient was withdrawn for reasons not included in the case report form.

7.1.3.2 Adverse events associated with dropouts

Two subjects discontinued the study due to significant adverse events. Randomized to atenolol, Subject 135, a 38 year old woman, received her first dose of study drug on June 28, 2003 and developed a toothache, thought to be moderate in intensity. She was treated with paracetamol and discontinued the study due to the toothache. Subject 286, a 27 year old woman, was randomized to placebo. After five days of treatment, she developed a headache and a fever of 101 degrees Fahrenheit. She received paracetamol for the headache, but she discontinued the study. Two days later, her symptoms resolved.

7.1.3.3 Other significant adverse events

The sponsor did not report any other significant adverse events.

7.1.4 Other Search Strategies

Please see Dr. Salma Lemtouni's Integrated Review of Safety for full details.

7.1.5 Common Adverse Events

There were 281 subjects in the safety population, and 45 (16%) of subjects complained of at least one adverse event (nebivolol 9/72 (12.5%)), atenolol 16/69 (23.2%), moxifloxacin 13/69

(18.8%), and placebo 7/71 (9.9%)). Of the 72 subjects exposed to nebivolol, 9 subjects reported at least one adverse event. Table 59 shows the number and percent of patients reporting these events in the nebivolol treatment group. Table 60 describes all adverse events reported in Study NEB-122.

Table 59. Adverse Events on Nebivolol (NEB-122)

Adverse Event	Nebivolol (N=72)
Abdominal cramps	1 (1.4%)
Dizziness	4 (5.6%)
Headache	2 (2.8%)
Nasal congestion	1 (1.4%)
Nausea	1 (1.4%)

(Adapted from Sponsor by Hicks K, Nebivolol, NDA 21,742)

Table 60. All Adverse Events Reported in NEB-122

Adverse Event	Nebivolol (N=72)	Atenolol (N=69)	Moxifloxacin (N=69)	Placebo (N=71)
Abdominal Cramps	1 (1.4%)	0	0	0
Backache	0	1 (1.4%)	0	0
Chest Pain	0	1 (1.4%)	0	0
Cold Sinus	0	0	1 (1.4%)	0
Constipation	0	2 (2.9%)	1 (1.4%)	0
Diarrhea	0	1 (1.4%)	1 (1.4%)	1 (1.4%)
Dizziness	4 (5.6%)	4 (5.8%)	6 (8.7%)	2 (2.8%)
Fatigue	0	1 (1.4%)	0	0
Feels Feverish	0	0	0	1 (1.4%)
Fever 101F	0	0	0	1 (1.4%)
Headache	2 (2.8%)	8 (11.6%)	3 (4.3%)	4 (5.6%)
Light-headed	0	1 (1.4%)	0	0
Lower abdominal pain	0	0	1 (1/4%)	0
Nasal congestion	1 (1.4%)	0	0	0
Nausea	1 (1.4%)	2 (2.9%)	6 (8.7%)	0
Nervousness	0	0	1 (1.4%)	0
Numbness in right arm	0	0	1 (1.4%)	0
Palpitations	1 (1.4%)	1 (1.4%)	1 (1.4%)	0
Rash	1 (1.4%)	0	1 (1.4%)	0
Rash on Buttock	1 (1.4%)	0	0	0
Sore Throat	0	0	0	1 (1.4%)
Stomach Ache	0	1 (1.4%)	0	0
Stomach Discomfort	0	0	1 (1.4%)	0
Stomach Pain	0	0	0	1 (1.4%)
Tachycardia	0	0	1 (1.4%)	0
Throat Ache	0	0	1 (1.4%)	0
Toothache	1 (1.4%)	1 (1.4%)	1 (1.4%)	0
Vaginal Rash	0	1 (1.4%)	0	0
Vomit	1 (1.4%)	1 (1.4%)	1 (1.4%)	0

(Independent analysis by Hicks K, Nebivolol, NDA 21,742)

One patient in the nebivolol treatment group experienced palpitations, but his electrocardiographic tracings were consistent with sinus rhythm during his symptoms.

Results

Primary QTc Results

The primary endpoint was the change in the average QTc interval from Day 0 to 2 hours after dosing on Day 7 and was not statistically significant between nebivolol and placebo by examination of least squares (LS) means. At this timepoint, however, the comparisons of Moxifloxacin vs. Placebo and Nebivolol vs. Moxifloxacin were statistically significant.
The sponsor performed the primary ECG analysis at this timepoint on 71, 60, 67, and 69 subjects on nebivolol, atenolol, moxifloxacin, and placebo, respectively. For the primary analysis, the sponsor used ANCOVA with treatment as factor and average baseline QTc and gender as the covariates. If the upper limit of the confidence interval was < 6 msec, the sponsor concluded nebivolol did not significantly prolong QTc, compared with placebo. Since Bazett's correction overcorrects at elevated heart rates and undercorrects at rates below 60 bpm, we concentrated our analyses on QTc using Fridericia's formula and the population correction factor, as seen in Table 61 below.

Table 61. QTc Interval Change from Day 0 to 2 Hours after Dosing on Day 7 (NEB-122)

QTc Parameter	Comparison	LS Mean of Test	LS Mean of Reference	Difference	95% C.I.[a]	p-value
Population Correction Factor	**Nebivolol vs. Placebo**	-5.0628	-6.2074	1.1446	-4.0907, 6.3779	0.6672
	Moxifloxacin vs. Placebo	5.2175	-6.2074	11.4249	6.0936, 16.7563	<0.0001
	Nebivolol vs. Moxifloxacin	-5.0628	5.2175	-10.280	-15.583, -4.9774	0.0002
	Nebivolol vs. Atenolol	-5.0628	-4.9142	-0.1486	-5.5762, 5.2790	0.9570
Fridericia's Formula[b]	**Nebivolol vs. Placebo**	-5.7041	-6.3817	0.6776	-4.5716, 5.9268	0.7996
	Moxifloxacin vs. Placebo	5.2976	-6.3817	11.6792	6.336, 17.0248	<0.0001
	Nebivolol vs. Moxifloxacin	-5.7041	5.2976	-11.002	-16.319, -5.6847	0.0001
	Nebivolol vs. Atenolol	-5.7041	-5.3953	-0.3088	-5.7508, 5.1332	0.9111

[a]C.I. = Confidence Interval
[b]Population correction factor = 0.329

(Reproduced from Choi J, Reviewer's Analysis, 2004, Statistical Review and Evaluation, Cardio-Renal Division, NDA 21,742, page 15 and Sponsor, NEB-122, Table 6, page 58)

At two hours post dosing on Day 7, the mean difference in QTcP between nebivolol and placebo was 1.14 msec, with a 95% confidence interval of (-4.09, 6.38). Using QTcF, the mean difference between nebivolol and placebo was 0.68 msec with a 95% confidence interval of (-4.5716, 5.9268). The sponsor concluded nebivolol did not significantly affect QTc.

At 2 hours post dosing on Day 7, there were no statistically significant differences between treatment groups in the number of subjects having clinically notable QTcF intervals or increases from baseline QTcF Intervals, as seen in Table 62.

Table 62. Subjects with Clinically Notable QTc-F Intervals or Increase from Baseline QTc-F Intervals at 2 Hours Post Dose on Day 7 (NEB-122)

QTc-F Signal Value	Nebivolol N=71	Atenolol N=60	Moxifloxacin N=67	Placebo N=69
	n (%) of subjects with abnormal QTc-F			
≥ 450 msec	1 (1.4%)	2 (3.3%)	2 (3.0%)	0 (0.0%)
p-value*		0.593	0.611	1.000
≥ 480 msec	0	0	0	0
≥ 500 msec	0	0	0	0
≥ 30 msec increase from baseline	2 (2.8%)	2 (3.3%)	7 (10.4%)	1 (1.4%)
p-value*		1.000	0.090	1.000
≥ 60 msec increase from baseline	0	0	0	0

* p-value for Fisher's Exact test comparing nebivolol to other treatments.
QTc-F = QT interval corrected for heart rate using Fridericia's formula
msec = milliseconds

(Reproduced from Sponsor, NEB-122, Table 8, Data Source: Appendix 15, Table 18, page 63)

Secondary QTc Results:

The secondary endpoint was the change in average QTc intervals from Day 0 to all other evaluation times, and the change in other ECG intervals (PR, RR, QRS, QT) and heart rate (HR) from Day 0 to all other evaluation times. At 2 hours post dosing on Day 7, Table 63 shows the mean changes from baseline in a variety of ECG parameters. At this point in time, atenolol appeared to have a greater effect on mean heart rate than nebivolol.

Table 63. Mean (SD) Change from Baseline in ECG Parameters at 2 Hours Post Dose on Day 7 (NEB-122)

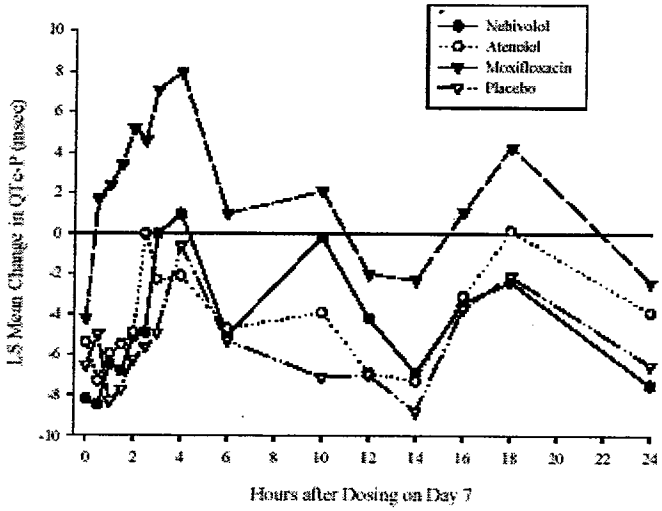
	Nebivolol (N = 71)	Atenolol (N = 60)	Moxifloxacin (N = 67)	Placebo (N = 67)
QTc-P (msec)	-5.1 (24.11)	-6.4 (18.66)	5.2 (19.37)	-8.6 (20.86)
QTc-F (msec)	-5.6 (23.78)	-6.9 (18.41)	5.3 (19.90)	-8.7 (20.92)
QTc-B (msec)	-18.4 (31.54)	-22.4 (21.60)	11.1 (24.83)	-5.9 (25.68)
QT (msec)	19.3 (26.57)	22.6 (28.70)	-5.0 (24.54)	-13.8 (27.49)
RR (msec)	175.2 (172.17)	204.0 (145.30)	-68.0 (124.58)	-39.6 (139.11)
PR (msec)	4.5 (15.57)	5.6 (17.49)	-3.3 (15.55)	-5.0 (16.37)
QRS (msec)	-3.1 (8.09)	-2.4 (8.45)	-6.3 (9.70)	-5.1 (8.76)
HR (bpm)	-12.6 (13.20)	-15.1 (12.06)	5.6 (11.91)	3.2 (13.82)

Data Source: Appendix 15, Table 6

(Reproduced from Sponsor, NEB-122, Table 7, page 61; Data Source: Appendix 15, Table 6)

In Figure 8, the sponsor graphically displays change in LS mean in QTc-P on Day 7 at all timepoints.

Figure 8. Graph of Changes of QTc on Day 7 (NEB-122)



(Reproduced from Sponsor, NEB-122, Figure 3, page 60; Data Source: Appendix 15, Tables 14.1-14.15)

The sponsor's analysis in Table 64 showed a statistically significant difference in LS mean change in QTcP at 10 hours post dosing on Day 7 between nebivolol and placebo ($p = 0.0146$ for QTcP and $p = 0.0255$ for QTcF).

Table 64. Pairwise Comparisons of QTc Interval Change from Day 0 to 10 Hours after Dosing on Day 7 (NEB-122)

QTc Parameter	Comparison	LS Mean of Test	LS Mean of Reference	Difference	95% C.I.[a]	p-value
Population Correction Factor[a]	Nebivolol vs. Placebo	-0.1690	-7.0564	6.8874	(1.3725, 12.4023)	0.0146
	Moxifloxacin vs. Placebo	2.1375	-7.0564	9.1939	(3.6215, 14,7663)	0.0013
	Nebivolol vs. Moxifloxacin	-0.1690	2.1375	-2.3065	(-7.8634, 3.2503)	0.4145
	Nebivolol vs. Atenolol	-0.1690	-3.9301	3.7611	(-1.9245, 9.4468)	0.1939
Fridericia's Formula[b]	Nebivolol vs. Placebo	-0.4105	-6.6806	6.2701	(0.7747, 11.7655)	0.0255
	Moxifloxacin vs. Placebo	2.3739	-6.6806	9.0545	(3.5018, 14.6071)	0.0015
	Nebivolol vs. Moxifloxacin	-0.4105	2.3739	-2.7844	(-8.3214, 2.7527)	0.3230
	Nebivolol vs. Atenolol	-0.4105	-4.1492	3.7387	(-1.9267, 9.4040)	0.1949

[a]C.I. = Confidence Interval
[b]Population correction factor = 0.329

(Reproduced from Sponsor, Appendix 15, Table 4.10, page 101)

In the sponsor's analysis, the change in QTc LS mean for nebivolol from baseline to 10 hours post dosing on Day 7 was only -0.1690 for QTcP and -0.4105 for QTcF. At this same timepoint, the change in QTc LS mean for placebo was -7.0564 for QTcP and -6.6806 for QTcF, which was associated with an increase in mean heart rate from approximately 73 bpm at baseline to 81 bpm at 10 hours post dosing on Day 7.

The increased heart rate in the placebo group, compared with nebivolol, was the driving force for statistical significance because the QTc interval decreased significantly in the placebo group, as seen in Table 65.

Table 65. Summary of ECG Parameters by Treatment and Time (24-Hour ECG) (NEB-122)

		Day 1, 0 hrs	Day 7, 2 hours	Day 7, 2.5 hours	Day 7, 3 hours	Day 7, 4 hours	Day 7, 10 hours	Day 7, 12 hours		Day 1, 0 hours	Day 7, 2 hours	Day 7, 2.5 hours	Day 7, 3 hours	Day 7, 4 hours	Day 7, 10 hours	Day 7, 12 hours
Parameter	Statistic	Nebivolol	Nebivolol	Nebivolol	Nebivolol	Nebivolol	Nebivolol	Nebivolol		Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo
Heart Rate	N	71	71	71	71	71	69	69		70	69	69	69	69	68	69
(bpm)	Mean (SD)	75.2 (12.76)	58.1 (7.96)	57.4 (7.29)	58.2 (9.10)	61.6 (8.06)	66.0 (9.19)	67.8 (9.21)		**73.0** (11.70)	74.9 (12.16)	74.5 (13.50)	73.9 (13.33)	81.0 (13.64)	**81.0** (13.23)	84.4 (15.44)
	Median (Min-Max)	74.0 (48-108)	57.0 (46-82)	59.0 (40-75)	56.0 (41-89)	62.0 (44-84)	66.0 (42-90)	66.0 (48-94)		73.5 (48-98)	74.0 (49-128)	74.0 (52-128)	74.0 (51-129)	81.0 (50-125)	80.0 (57-116)	83.0 (56-122)
	95% CI	72.14-78.17	56.23-60.00	55.68-59.14	56.04-60.35	59.66-63.47	63.81-68.22	65.56-69.98		70.24-75.82	71.98-77.82	71.28-77.77)	70.67-77.07	77.74-84.29	77.83-84.23)	80.71-88.13
RR Interval	N	71	71	71	71	71	69	69		70	69	69	69	69	68	69
(msec)	Mean (SD)	821.8 (139.79)	1052 (135.90)	1065 (143.19)	1056 (154.83)	992.9 (134.11)	929.0 (142.38)	902.5 (121.61)		844.3 (143.58)	822.3 (128.45)	830.0 (142.36)	837.2 (143.66)	762.2 9132.18)	759.3 (121.74)	734.0 (132.09)
	Median (Min-Max)	809.0 (554-1260)	1054.0 (729-1301)	1022.0 (801-1484)	1066.0 (675-1458)	968.0 (716-1366)	903.0 (666-1444)	910.0 (637-1248)		816.0 (611-1248)	815.0 (467-1238)	811.0 (469-1149)	814.0 (464-1184)	745.0 (481-1192)	750.5 (518-1060)	725.0 (490-1078)
	95% CI	788.73-854.91	1020.1-1084.4	1031.5-1099.3	1019.0-1092.3	961.13-1024.6)	894.80-963.20	873.32-931.75		810.04-878.51)	791.45-853.16	795.76-864.16	802.72-871.74	730.42-793.93	729.83-788.76	702.30-765.76
QT Interval	N	71	71	71	71	71	69	69		70	69	69	69	69	68	69
(msec)	Mean (SD)	369.7 (22.22)	401.3 (25.77)	402.8 (25.73)	406.1 (26.38)	399.5 (25.45)	390.7 (27.17)	382.7 (22.52)		**377.5** (27.75)	368.8 (28.86)	371.0 (28.93)	372.1 (28.92)	364.9 (31.96)	**358.9** (22.96)	354.8 (26.31)
	Median (Min-Max)	368.0 (325-432)	404.0 (353-456)	401.0 (355-471)	405.0 (356-473)	397.0 (350-451)	388.0 (341-474)	381.0 (336-455)		374.5 (329-488)	374.0 (298-468)	375.0 (297-452)	374.0 (293-447)	362.0 (286-465)	359.0 (310-415)	354.0 (293-423)
	95% CI	364.43-374.95	395.18-407.38	396.76-408.93	399.90-412.39	393.48-405.53	384.12-397.18	377.31-388.13		370.93-384.16	361.85-375.72	364.01-377.91	365.15-379.05)	357.22-372.58	353.37-364.48	348.49-361.13
QTcP	N	71	71	71	71	71	69	69		70	69	69	69	69	68	69
(msec)	Mean (SD)	396.0 (17.85)	395.7 (21.84)	395.6 (19.39)	400.4 (23.50)	401.6 (22.46)	401.3 (19.60)	397.0 (20.38)		**400.7** (24.01)	394.6 (23.09)	395.8 (22.57)	396.0 (23.92)	400.1 (23.68)	**394.3** (21.50)	394.4 (21.71)
	Median (Min-Max)	394.0 (348-445)	394.1 (346-459)	392.8 (361-441)	401.3 (350-448)	401.2 (357-461)	401.4 (360-444)	394.6 (356-445)		399.6 (351-475)	395.2 (344-443)	392.4 (349-443)	398.5 (339-445)	401.8 (338-452)	394.1 (337-439)	397.2 (337-449)
	95% CI	391.76-400.21	390.54-400.88	391.05-400.23	394.86-405.99	396.27-406.90	396.62-406.04	392.14-401.93		394.99-406.44	389.03-400.12	390.38-401.23	390.26-401.75	394.44-405.81)	389.12-399.53	389.21-399.64
QTcF	N	71	71	71	71	71	69	69		70	69	69	69	69	68	69
(msec)	Mean (SD)	396.5 (18.00)	395.3 (21.94)	395.1 (19.07)	400.3 (23.47)	401.7 (22.47)	401.4 (19.41)	397.2 (20.35)		**401.0** (24.25)	394.7 (22.97)	396.1 (22.71)	396.4 (23.99)	400.6 (23.68)	**395.0** (21.71)	394.8 (21.86)
	Median (Min-Max)	395.0 (347-445)	394.0 (347-460)	391.0 (360-439)	399.0 (350-447)	401.0 (356-460)	402.0 (360-444)	394.0 (357-446)		399.5 (352-476)	395.0 (345-443)	393.0 (349-444)	399.0 (339-446)	402.0 (339-453)	395.0 (336-440)	397.0 (339-450)
	95% CI	392.19-400.71	390.15-400.53	390.63-399.65	394.73-405.84	396.38-407.02	396.70-406.03	392.27-402.05		395.25-406.81	389.15-400.18	390.63-401.54	390.64-402.17	394.86-406.24	389.71-400.23	389.52-400.02

(Compiled by Hicks K from NEB-122, Appendix 15, Table 5, Summary of ECG Parameters by Treatment and Time—24 hour ECG, pages 107-226)

Ms. Choi of the Cardio-Renal Division obtained different p-values in her independent review of the data. Not only did she find a significant difference in LS mean change of nebivolol compared with placebo on Day 7 at 10 hours, but she also found a significant difference in QTcP on Day 7 at 3 hours which was gender-driven. Although the difference in QTcF was not statistically significant, there was a trend towards significance with p = .0643. Ms. Choi's independent analysis of QTcF and QTcP is shown in Table 66 below.

Table 66. QTc Changes from Baseline on Day 7 (NEB-122)

	LS mean change of Nebivolol	LS mean change of Placebo	Difference	95% Confidence Interval	p-value
Fridericia's Formula					
0 hour	-7.9268	-5.8803	-2.0465	-7.5435, 3.4505	0.4669
0.5 hour	-8.8581	-4.8994	-3.9588	-9.2241, 1.3065	0.1429
1 hour	-7.1297	-8.1466	1.0170	-3.7217, 5.7556	0.6747
1.5 hour	-6.9671	-7.4315	0.4644	-5.1234, 6.0523	0.8708
2 hour	-5.8088	-6.2377	0.4290	-4.8881, 5.7461	0.8746
2.5 hour	-5.6669	-5.3043	-0.3627	-5.3847, 4.6593	0.8877
3 hour	**0.1767**	**-4.4557**	4.6324	-0.2341, 9.4989	**0.0643**
4 hour	0.4766	-0.4531	0.9297	-4.3343, 6.1937	0.7298
6 hour	-4.8953	-4.5991	-0.2962	-5.7448, 5.1524	0.9153
10 hour	**-0.0053**	**-6.3171**	6.3117	0.6085, 12.0149	**0.0319**
12 hour	-4.2940	-6.7354	2.4414	-2.5734, 7.4563	0.3417
14 hour	-7.3824	-8.2778	6.7669	-0.5302, 14.0640	0.7368
16 hour	-3.2928	-3.4307	0.1379	-4.8405, 5.1143	0.9568
18 hour	-2.3628	-1.5783	-0.7844	-6.2866, 4.7177	0.7804
24 hour	-7.9335	-5.9069	-2.0266	-7.7041, 3.6509	0.4854
Population Correction Factor					
0 hour	-7.9672	-6.0379	-1.9293	-3.5603, 7.4189	0.4921
0.5 hour	-8.5128	-4.9225	-3.5902	-8.8377, 1.6573	0.1822
1 hour	-6.4415	-8.2220	1.7805	-2.9121, 6.4731	0.4584
1.5 hour	-6.6070	-7.4476	0.8405	-4.6971, 6.3781	0.7665
2 hour	-5.2825	-6.2003	0.9189	-4.4307, 6.2685	0.7372
2.5 hour	-5.0964	-5.2357	0.1393	-4.9392, 5.2179	0.9572
3 hour	**0.5771**	**-4.5224**	5.0995	0.2614, 9.9376	**0.0408**
4 hour	0.6323	-0.5466	1.1789	-4.1068, 6.4646	0.6627
6 hour	-4.6468	-4.9100	0.2632	-5.1683, 5.6948	0.9245
10 hour	**0.2164**	**-6.5050**	6.7214	1.0155, 12.4274	**0.0225**
12 hour	-4.1912	-6.7322	2.5409	-2.4455, 7.5273	0.3197
14 hour	-7.1203	-8.5689	1.4486	-3.7401, 6.6373	0.5852
16 hour	-3.5118	-3.4542	-0.0575	-5.0465, 4.9315	0.9820
18 hour	-2.0696	-1.7131	-0.3564	-5.8754, 5.1626	0.8995
24 hour	-7.5915	-6.1133	-1.4782	-7.1416, 4.1852	0.6098

(Reproduced from Choi J, Reviewer's Analysis, 2004, Statistical Review and Evaluation, Cardio-Renal Division, NDA 21,742, Independent Analysis, NEB-122, page 17)

Ms. Choi found a statistically significant gender effect (p = 0.0017) in NEB-122. At both 3 and 10 hours on Day 7, women in the nebivolol treatment group had significant increases in QTcP (p = 0.0129 and 0.0267, respectively) and QTcF (p = 0.0167 and 0.0338, respectively), compared with the placebo group, as seen in Table 67 and Table 68. The LS mean change in QTcF interval

at 3 hours post dosing on Day 7 was 6.5569 for women on nebivolol, compared with -2.5777 for placebo. At 10 hours, the LS mean change in QTcF was 0.56613 for women on nebivolol, compared with -8.4570 for placebo. In women on nebivolol at 3 hours post dosing on Day 7, LS mean change in QTcP was 6.9322, compared with -2.5293 for placebo. At 10 hours, women on nebivolol had a LS mean change in QTcP of 0.7567, compared with -8.6672 for placebo.

Table 67. QTc Changes by Gender at 3 Hours and 10 Hours on Day 7 (Fridericia's Formula) (NEB-122)

	LS Mean Change of Nebivolol	LS Mean Change of Placebo	Difference	95% Confidence Interval	p-value
3 hours on Day 7					
Male	-5.6326	-6.7841	1.1516	-5.3517, 7.6549	0.7295
Female	6.5569	-2.5777	9.1346	1.8760, 16.3932	**0.0167**
Male and Female	0.1767	-4.4557	4.6324	-0.2341, 9.4989	0.0643
10 hours on Day 7					
Male	-0.7559	-5.4496	4.6937	-3.1398, 12.5272	0.2440
Female	0.56613	-8.4570	9.0231	0.8936, 17.1526	**0.0338**
Male and Female	-0.0053	-6.3171	6.3117	0.6185, 12.0149	0.0319

(Reproduced from Choi J, Reviewer's Analysis, 2004, Statistical Review and Evaluation, Cardio-Renal Division, NDA 21,742, Independent Analysis, NEB-122, page 18)

Table 68. QTc Changes by Gender at 3 Hours and 10 Hours on Day 7 (Population Correction Factor) (NEB-122)

	LS Mean Change of Nebivolol	LS Mean Change of Placebo	Difference	95% Confidence Interval	p-value
3 hours on Day 7					
Male	-5.2347	-6.9539	1.7192	-4.7449, 8.1833	0.6037
Female	6.9322	-2.5293	9.4615	2.2391, 16.6839	**0.0129**
Male and Female	0.5771	-4.5224	5.0995	0.2614, 9.9376	0.0408
10 hours on Day 7					
Male	-0.5078	-5.6206	5.1128	-2.7396, 12.9651	0.2059
Female	0.7567	-8.6672	9.4239	1.3086, 17.5394	**0.0267**
Male and Female	0.2164	-6.5050	6.7214	1.0155, 12.4274	0.0225

(Reproduced from Choi J, Reviewer's Analysis, 2004, Statistical Review and Evaluation, Cardio-Renal Division, NDA 21,742, Independent Analysis, NEB-122, page 18)

The significant effect at 3 hours cannot be explained by heart rate, as seen in Table 69. If heart rate and bradycardia were the etiology, we would also expect to see increases in QTcF and QTcP in men, but this is not the case. Clearly, women experienced an increase in QTcF and QTcP at 3 hours post dosing on Day 7, but the QTc never exceeded 420 msecs. Although this increase in QTc may represent an effect from nebivolol, it could also be consistent with a random sampling effect, as there were no other consistent increases in QTc throughout the study. Furthermore, a QTc of 420 msecs is within normal limits.

Table 69. Gender Effect on Heart Rate, QTcF, and QTcP (NEB-122)

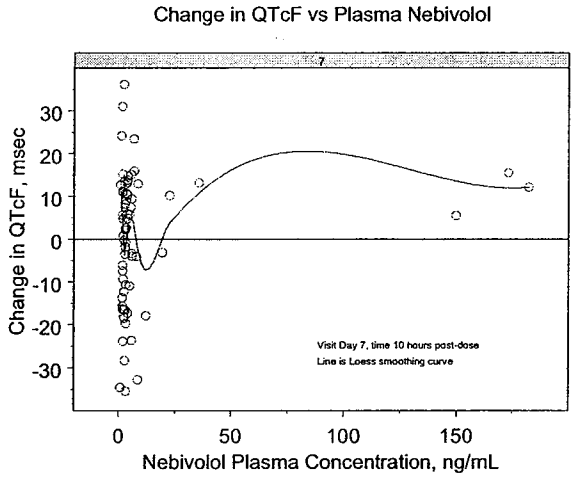
	Heart Rate/Change in Heart Rate (bpm)		QTcF/Change in QTcF (msec)		QTcP/Change in QTcP (msec)	
	Nebivolol	**Placebo**	**Nebivolol**	**Placebo**	**Nebivolol**	**Placebo**
Baseline						
Female	74.45	74.65	410.48	412.51	410.12	412.08
Male	71.40	71.42	395.80	393.00	394.41	392.65
Day 7, 2.5 hours						
Female	-17.01	2.60	-4.74	-4.92	-4.19	-4.98
Male	-14.63	0.64	-7.18	-6.44	-6.56	-6.24
Day 7, 3 hours						
Female	**-13.06**	1.96	6.56	-2.58	**6.93**	-2.53
Male	**-16.09**	-0.001	-5.63	-6.78	**-5.24**	-6.95
Day 7, 4 hours						
Female	-11.77	6.19	3.84	-1.61	4.09	-1.66
Male	-11.19	9.72	-2.29	0.23	-2.23	0.07

(Independent Analysis from Choi J, provided in e-mail dated 21 October 2004)

Nebivolol Plasma Concentration

There was no relationship between the plasma concentration of nebivolol and QTcF on days 1, 4, and 7 of dosing. Plasma concentration results for nebivolol on Day 7 are shown in Figure 9.

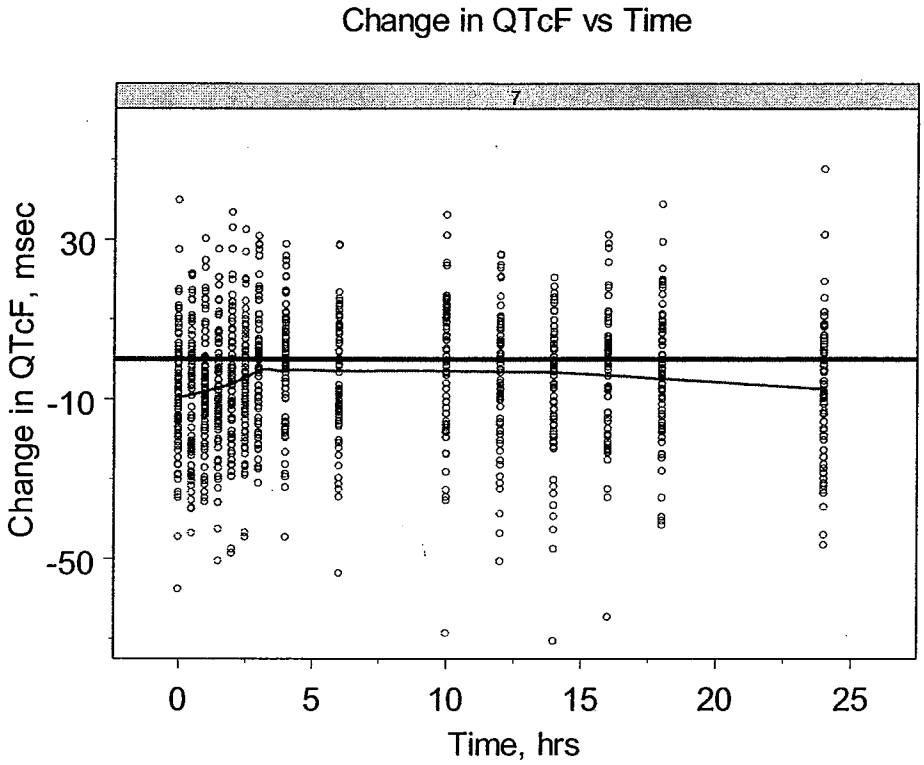
Figure 9. Change in QTcF vs. Plasma Nebivolol on Day 7 (NEB-122)



(Reproduced from Mishina E, Independent Analysis, 2004, Biopharmacology Review, Cardio-Renal Division, NDA 21,742, NEB-122, e-mail communication dated 18 October 2004)

Additionally, there was no significant change in QTcF over time on Day 7 of dosing, as seen in Figure 10.

Figure 10. Change in QTcF vs. Time on Day 7 (NEB-122) (The Curve is Loess Smoothing Line)



(Reproduced from Mishina E, Independent Analysis, 2004, Biopharmacology Review, Cardio-Renal Division, NDA 21,742, NEB-122, page 119 of 140)

According to Elena Mishina, Ph.D., there was no significant effect of nebivolol plasma concentration on change in QTcF by gender.

Extensive versus Poor Metabolizers

In NEB-122, there were three poor metabolizers in both the nebivolol and atenolol treatment groups. Mean peak plasma concentrations on Day 7 for *d*-nebivolol ranged from 6.8 to 54.5 ng/mL and for *l*-nebivolol ranged from 11.6 to 126 ng/mL. On Day 7, Tmax for the poor metabolizers in the nebivolol treatment group was 1.5 hours in one subject and 6 hours in the two other subjects.

Laboratory Abnormalities

Both nebivolol and placebo treatment groups developed marked increases in triglycerides from screening to end of study. At screening, mean triglycerides (SD) in the nebivolol and placebo groups were 152.39 (92.489) and 164.83 (111.68), respectively. At study completion, mean triglycerides in the nebivolol and placebo groups were 201.28 (42.228) and 209.97 (32.687), respectively. Additionally 5/6 patients in the nebivolol treatment group had increases in serum glucose at the end of study, compared with screening. Chemistry abnormalities occurring in at least 3% of subjects at the end of study are shown in Table 70.

Table 70. Incidence of Chemistry Abnormalities occurring in at Least 3% of Subjects at the End of the Study (NEB-122)

Parameter	Nebivolol N=72	Atenolol N=71	Moxifloxacin N=69	Placebo N=69
	n (%) of Subjects with Abnormal Value			
CO_2	1 (1.4%)	3 (4.3%)	1 (1.4%)	0 (0.0%)
Glucose	6 (8.3%)	3 (4.3%)	3 (4.3%)	4 (5.6%)
BUN	3 (4.2%)	1 (1.4%)	2 (2.9%)	4 (5.6%)
Cholesterol	8 (11.1%)	14 (20.3%)	10 (14.5%)	20 (28.2%)
Triglycerides	10 (13.9%)	13 (18.8%)	9 (13.0%)	6 (8.5%)
ALT	4 (5.6%)	5 (7.2%)	1 (1.4%)	4 (5.6%)

Data Source: Appendix 15, Table 13.1

(Reproduced from Sponsor, NEB-122, Table 10, page 70)

At the end of the study, 112, 94, and 53 subjects had decreased red blood cells, hemoglobin, and hematocrit, respectively. The sponsor attributed these findings to phlebotomy. Hematology abnormalities seen in at least 3% of subjects at study completion are shown in Table 71 below.

Table 71. Incidence of Hematology Abnormalities Occurring in at Least 3% of Subjects at the End of the Study (NEB-122)

Parameter	Nebivolol N=72	Atenolol N=71	Moxifloxacin N=69	Placebo N=69
	n (%) of Subjects with Abnormal Value			
Hemoglobin	20 (27.8%)	28 (40.6%)	23 (33.3%)	22 (31.0%)
Hematocrit	10 (13.9%)	13 (18.8%)	14 (20.3%)	15 (21.1%)
RBC	26 (36.1%)	25 (36.2%)	26 (37.7%)	26 (36.6%)
Neutrophils (%)	4 (5.6%)	3 (4.3%)	1 (1.4%)	4 (5.6%)
Lymphocytes (%)	7 (9.7%)	4 (5.8%)	3 (4.3%)	6 (8.5%)
Platelets	0 (0.0%)	1 (1.4%)	3 (4.3%)	3 (4.2%)
MCV	0 (0.0%)	1 (1.4%)	1 (1.4%)	3 (4.2%)
MCH	1 (1.4%)	2 (2.9%)	2 (2.9%)	3 (4.2%)
MC HGB Conc.	9 (12.5%)	3 (4.3%)	3 (4.3%)	5 (7.0%)

MCV = Mean corpuscular volume; MCH = Mean corpuscular hemoglobin;
MC HGB Conc. = mean corpuscular hemoglobin concentration

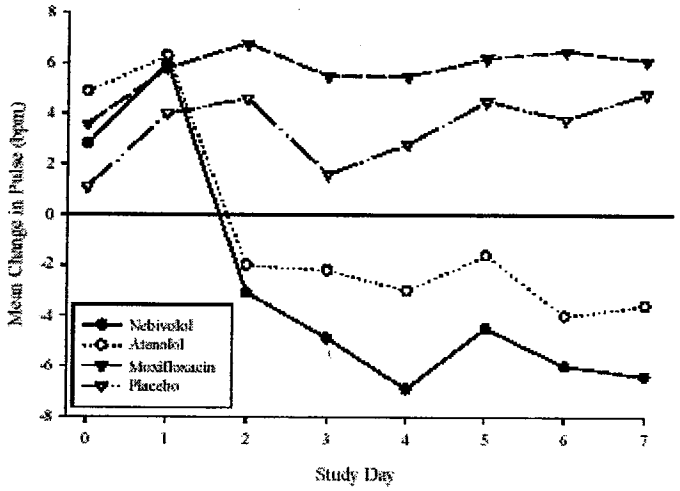
Data Source: Appendix 15, Table 15.1

(Reproduced from Sponsor, NEB-122, Table 11, page 71)

Effect on Blood Pressure and Heart Rate

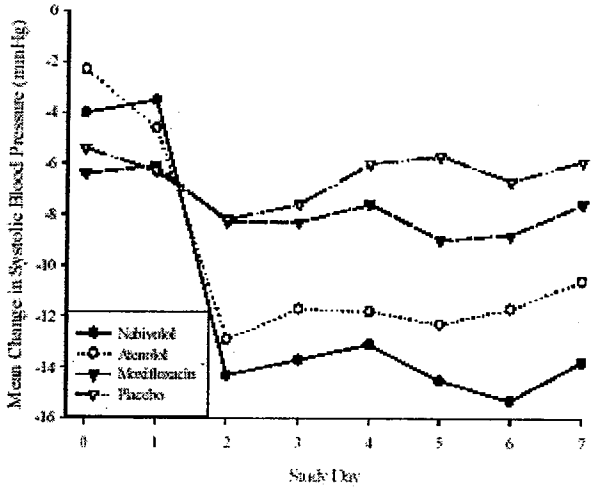
Although diastolic and systolic blood pressures in nebivolol-treated patients slightly increased on day 7, nebivolol otherwise decreased heart rate, systolic blood pressure, and diastolic blood pressure over the course of the study, as seen in Figures 11 through 13. These effects on blood pressure and heart rate support the results presented in the integrated review of efficacy.

Figure 11. Mean Change from Baseline Pulse by Study Day and Treatment (NEB-122)



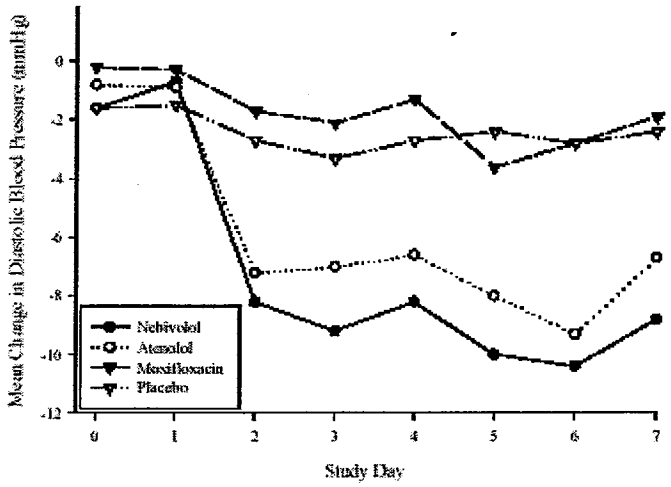
(Reproduced from Sponsor, NEB-122, Figure 4, page 73)

Figure 12. Mean Change from Baseline Systolic Blood Pressure by Study Day and Treatment (NEB-122)



(Reproduced from Sponsor, NEB-122, Figure 5, page 73)

Figure 13. Mean Change from Baseline Diastolic Blood Pressure by Study Day and Treatment (NEB-122)



(Reproduced from Sponsor, NEB-122, Figure 6, page 74)

Summary (NEB-122)

Nebivolol did not appear to have any significant effect on QTc, with the exception of Day 7, 3 hours, when women in the nebivolol treatment group significantly increased QTcP and QTcF, compared with placebo. Despite the increase in QTc, the QTc interval itself was not prolonged. Either this timepoint represents a true QT effect of nebivolol or is consistent with random chance. There does not appear to be any other consistent QT effects in this study.

NEB-122 has several shortcomings. First, the study was not blinded. Second, the study design did not allow for correct dosing of the positive control (moxifloxacin). Patients in the moxifloxacin treatment group received 7 days of moxifloxacin, instead of the typical single dose. Because of the chronic dosing, we cannot determine whether or not moxifloxacin truly prolonged the QTc and was an adequate positive control. Third, the study was not of sufficient length to evaluate QT effects in poor metabolizers. There were only 3 poor metabolizers studied in each of the nebivolol and atenolol treatment groups, and the Tmax varied tremendously between individuals. Since the half-life of *d*-nebivolol is approximately 13 hours, if we estimate the half-life for poor metabolizers as 4-fold the half-life of nebivolol, the estimated half-life for poor metabolizers is approximately 52 hours. Steady-state for poor metabolizers would be reached in approximately four to five half-lives or 208 to 260 hours, which is 8.7 to 10.8 days. The QT study for poor metabolizers, therefore, is inadequate, because patients only received study drug for 7 days. Because nebivolol has many metabolites with poorly characterized half-lives, it is uncertain whether or not we would see consistent increases in QTc if the study was continued for a longer period of time.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Please see Section 1.3.4.

8.2 Drug-Drug Interactions

Please see Section 1.3.5.

8.3 Special Populations

Please see Section 1.3.6.

8.4 Pediatrics

The Cardio-Renal Division granted the sponsor a three-year deferral for the use of nebivolol in pediatric hypertensive patients, ages 0 through 16 years. The sponsor submitted a proposed pediatric development plan and requested a pediatric waiver for nebivolol on December 21, 2004.

8.5 Advisory Committee Meeting

Not required at this time.

8.6 Postmarketing Risk Management Plan

Please see Section 1.2.1.

8.7 Other Relevant Materials

Please see References and Reviews of Supportive Studies.

9 OVERALL ASSESSMENT

9.1 Conclusions

The sponsor demonstrated the efficacy of nebivolol in 6 Pivotal Trials. Preclinical studies in mice show nebivolol was strongly associated with the development of Leydig cell tumors. The relevance of these preclinical findings to humans is uncertain. I consider nebivolol approvable only if the sponsor can clearly demonstrate nebivolol is not carcinogenic in humans.

9.2 Recommendation on Regulatory Action

Nebivolol is approvable for the treatment of mild to moderate hypertension, pending the following results:

1. Within the next two months, the sponsor plans to perform mechanistic studies in mice and rats to explain the development of Leydig cell tumors. If the sponsor proves nebivolol is not potentially carcinogenic in humans, the application is approvable.
2. Through consultative review, the Division of Reproductive and Urologic Drug Products will assist the Cardio-Renal Division in identifying the most sensitive markers for drug-related estrogenic effects in humans and in determining whether or not these markers predict the development of subsequent malignancies.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

Please see Section 1.2.1.

9.3.2 Required Phase 4 Commitments

Please see Section 1.2.2.

9.3.3 Other Phase 4 Requests

Please see Section 1.2.3.

9.4 Labeling Review

Line-by-line labeling review is pending the final Agency decision regarding approvability.

9.5 Comments to Applicant

None.

10 APPENDICES

11 REVIEW OF INDIVIDUAL STUDY REPORTS

In this section, I individually review the six pivotal studies as well as the studies to which I referred in the body of my efficacy review.

11.1 NEB-302 (Pivotal) ("A Double-Blind, Multi-Center, Randomized, Placebo-Controlled, Parallel Group Dosing Study Evaluating the Effects of Nebivolol on Blood Pressure in Patients with Mild to Moderate Hypertension")

Investigators

The 83 investigators are listed in Table 72 below. All 68 sites were in the US. Individual sites (n=68) randomized between 0 and 71 patients.

Table 72. Investigators (Study NEB-302)

Investigator	Site	# Pts	Investigator	Site	# Pts
		13			9
		24			3
		3			6
		2			23
		0			9
		0			16
		4			0
		5			06
		7			22
		15			5
		0			0
		0			0
		0			7
		3			6
		1			9
		0			31
		4			2
		3			47
		20			11
		0			33
		22			0
		7			53
		20			9
		0			9
		2			3

(continued)

Table 72. Investigators (Study NEB-302) (continued)

Investigator	Site	# Pts	Investigator	Site	# Pts
		25			71
		67			3
		32			4
		28			11
		13			1
		3			11
		14			0
		3			0
		18			7
		18			7
ed		24			8
		2			12
	K	3			6
		9			14
		7			6
		5			7
		0			

Study dates

September 19, 2001 – March 21, 2003

Study design

This study description was based upon the protocol dated June 5, 2000, the final protocol dated June 13, 2001, and amendments dated July 27, 2001[21] and March 13, 2002.[22]

This was a Phase III double-blind, multi-center, randomized, placebo-controlled, parallel group dosing study. The study had two phases. Phase I consisted of screening, followed by washout/single-blind placebo run-in (28-42 days). If patients previously on other antihypertensive medication did not satisfy inclusion criteria after 28 days, they were allowed an additional 14 days of single-blind placebo run-in. After successful completion of Phase I, patients entered the double-blind Phase II and were randomized to placebo or nebivolol 1.25, 2.5, 5, 10, 20, or 40 mg orally qd for 84 days. Patients randomized to nebivolol 40 mg were first initiated on 30 mg. If at two weeks these patients had a sitting heart rate at trough exceeding 55 bpm, the nebivolol dose was increased to 40 mg. The study included seven scheduled follow-up

[21] **The first amendment made a variety of minor changes, including using 1.25 mg tablets for the 2.5 mg dosage. Additionally, the sponsor clarified blood pressure inclusion criteria for patients receiving antihypertensive therapy and defined systolic blood pressure warning levels.**

[22] **The second amendment revised body mass index (BMI) from ≥ 35 to > 35 kg/m2 to reflect the new definition of obesity, as recommended by the National Institute of Health. Additionally, centrally acting alpha agonists became prohibited medications. In Amendment 2, the sponsor clarified the use of non-steroidal anti-inflammatory drugs (NSAIDs), acetylsalicylic acid, short acting nitrates, decongestants and antihistamines, acetaminophen, and serotonin selective receptor inhibitors (SSRI). In Amendment 2, investigators were instructed to call Teletrial® prior to drawing labs.**

Study design (continued)
visits, in addition to Visit 2a, if necessary, to assess eligibility. Following randomization (visit 3), scheduled follow-up was biweekly for the first month and then monthly thereafter. The goal was to randomize 75 patients in the placebo and nebivolol 1.25 and 2.5 mg groups as well as 150 patients in the nebivolol 5, 10, 20, and 40 mg groups.

Baseline assessments included history, physical exam, 12-lead ECG, beta-HCG urine pregnancy test (for women), routine laboratory evaluation, and genomics testing for cytochrome P450-2D6 analysis.

Study drug was to be taken between 7 AM and 10 AM each day with or without breakfast. On clinic days, study drug administration was deferred until the investigator obtained trough blood pressure and heart rate measurements. The investigator measured trough vital signs during all 7 clinic visits and peak vital signs during Visit 3 (Day 0) and Visit 7 (Day 84). At Study Visits 5 and 7, investigators performed pharmacokinetic sampling at trough (prior to dosing) and peak (2-3 hours post dosing). Pharmacokinetic samples measured plasma concentrations of *d*-nebivolol, *l*-nebivolol, nebivolol (sum of *d*- and *l*-nebivolol), and nebivolol glucuronides (the glucuronide conjugates of the *d*-and *l*-nebivolol enantiomers).

Inclusion Criteria for Study NEB-302 (Reproduced from Sponsor, page 30)

- Written informed consent.
- Age $\geq$ 18.
- High probability for compliance and study completion.
- Adult ambulatory patients with mild to moderate hypertension:
  - At Visit 1 (day -42 to -28), an average sitting diastolic blood pressure of $\geq$ 95 mm Hg and $\leq$ 109 mm Hg if not currently receiving antihypertensive treatment
  - At Visit 2 (day -28 to -14), an average sitting diastolic blood pressure of > 80 mm Hg and $\leq$ 109 mm Hg if patient currently receiving antihypertensive therapy treatment
- Patients currently receiving antihypertensive treatment with an average sitting diastolic blood pressure $\leq$ 80 mm Hg were permitted to continue the screening process only if the adverse event profile of their current antihypertensive medication(s) warranted a change in drug treatment.
- At randomization, Visit 3 (day 0), an average sitting diastolic blood pressure of $\geq$ 95 mm Hg and $\leq$ 109 mm Hg.

Exclusion Criteria for Study NEB-302 (Reproduced from Sponsor, page 30)

- Secondary hypertension
- Malignant hypertension (retinal hemorrhage, exudates, or papillary edema)
- History or presence of asthma, bronchospasm, or chronic obstructive airway disease
- Bradycardia (heart rate < 50 bpm) at rest in the supine position prior to randomization
- Chronic atrial fibrillation or recurrent tachyarrhythmia

Exclusion Criteria for Study NEB-302 (Reproduced from Sponsor, page 30)(continued)

- Sick sinus syndrome, including second or third degree AV block
- Diabetics with HbA1c $\geq$ 10% during the screening period
- History of sensitivity or significant adverse reaction to beta-blockers
- Myocardial infarction or cerebrovascular accident within 6 months of screening Visit 1. If the screening Visit 1 ECG exhibited diagnostic pathological Q waves and the timing of the event associated with these Q waves was unknown, the patient was excluded.
- Heart failure requiring treatment. A left ventricular ejection fraction of $\geq$ .040, if measured within 12 months of the trial.
- Hemodynamically significant valvular heart disease
- Presence of severe peripheral vascular disease
- Any major contraindication to stopping antihypertensive medications for a period of up to 18 weeks
- Significant thyroid, renal, or hepatic disease (TSH > 1.5 times the upper limit of normal, urine protein > 1+, creatinine > 2.2 mg/dL, AST [SGOT] and/or ALT [SGPT] greater than twice the upper limit of normal)
- A positive pregnancy test (beta-HCG) result, or a nursing female patient, or a female of childbearing potential who was not using appropriate contraception as determined by the principal investigator.
- Presence of any condition that in the judgment of the investigator, may have jeopardized the participant's adherence to the protocol or ability to complete the trial
- Concomitant therapy with at least one of the prohibited or restricted medications that may have affected blood pressure
- BMI $\geq$ 35 kg/m^2 and obesity as measured by waist circumference > 102 cm (40 inches) in men or > 88 cm in women
- Investigational drug use within 30 days of signing the informed consent
- Previous exposure to nebivolol for the treatment of hypertension
- Exaggerated systolic hypertension defined as an average sitting systolic blood pressure > 199 mm Hg

Prohibited Medications in Study NEB- 302 (Reproduced from Sponsor, page 35)

- Oral and ophthalmic beta-adrenergic blocking agents (e.g., atenolol, metoprolol, propranolol, timolol)
- Angiotensin converting enzyme inhibitors (ACEI, e.g., enalapril, captopril, ramipril)
- Angiotensin II receptor blockers (ARB, e.g., losartan, valsartan)
- Calcium channel blockers (CCB, e.g., amlodipine, diltiazem, nifedipine, verapamil, nicardipine, and felodipine)
- Alpha-1 receptor blockers (e.g., phentolamine, phenoxybenzamine, terazosin).
- Diuretics (e.g., furosemide, hydrochlorothiazide, spironolactone)
- Medications possibly affecting blood pressure (e.g., all anti-depressants with blood pressure altering effects including tricyclic anti-depressants and MAO inhibitors).
- Theophylline or beta-agonists.
- Drugs liable to cause salt retention (e.g., systemic corticosteroids)
- Long-acting oral nitrates (e.g., Isordil®, isosorbide dinitrate)

Prohibited Medications in Study NEB-302 (Reproduced from Sponsor, page 35)(continued)

- Treatment with a protease inhibitor within 180 days of the initiation of screening.
- Centrally acting alpha agonists (e.g., clonidine hydrochloride).

Restricted medications in Study NEB-302 (As stated on page 36)

- Non-steroidal anti-inflammatory drugs (NSAIDs): patients could not exceed 5 consecutive days of NSAID use. For 3 days prior to Visits 3 (Randomization) and 7 (Study Day 84), patients could not use NSAIDs.
- Acetylsalicylic acid: patients could not use acetylsalicylic acid in excess of 162 mg daily.
- Short acting nitrates (sublingual nitroglycerin): patients could not use short acting nitrates within 4 hours of clinic visits.
- Decongestants and antihistamines: once enrolled, patients could not use these agents within 3 days of Visits 3 (Randomization) and 7 (Study Day 84).
- Selective serotonin reuptake inhibitors (SSRIs): patients could use SSRIs only if the patient was on a stable dose for at least 3 months prior to Visit 1, was known to be compliant on the medication, and agreed to maintain this current stable dose for the study duration.

Major Protocol Violations (Reproduced from Sponsor, page 57)

- No informed consent
- Mean sitting DBP (trough) at Baseline < 95 mm Hg
- Mean sitting DBP (trough) at Baseline > 109 mm Hg
- Secondary hypertension
- Use of concomitant antihypertensive medications within 14 days of double-blind treatment or at any time thereafter
- Screening period < 14 days
- Trough blood pressure measurements taken < 22 or > 28 hours post-dosing at last clinic visit
- Peak blood pressure measurements taken < 2 or > 3 hours post-dosing at last clinic visit
- Study visit > 3 days before or after target date
- Baseline sitting DBP at trough performed > 2 days before first dose
- Received incorrect treatment (i.e., incorrect bottle dispensed)

Protocol Deviations (Reproduced from Sponsor, page 57)

- Bradycardia (average supine heart rate < 50 bpm at baseline)
- Sick sinus syndrome
- CHF requiring treatment at baseline
- Creatinine > 2.2 mg/dL at baseline
- SGOT or SGPT 2X ULN at baseline
- Significant thyroid disease (TSH 1.5 X ULN) at baseline
- Pregnancy
- Concomitant NSAIDS

In patients with mild to moderate hypertension, the sponsor's objectives were to determine if nebivolol was superior to placebo for treatment of elevated blood pressure, to determine the dose-response relationship of nebivolol on blood pressure, and to compare the safety and efficacy of nebivolol in both poor and extensive metabolizers.

The primary endpoint was change of the average sitting diastolic blood pressure taken at trough drug plasma level (24 ± 2 hours post-previous morning's dose) at the end of treatment (Day 84) compared to baseline.

The primary analysis was intention-to-treat (ITT) with the last observation carried forward (LOCF). Overall treatment effect was to be assessed after adjustment for baseline differences. Patients were stratified across all treatment arms by the following factors in decreasing priority: metabolism of nebivolol (poor metabolizer (PM) versus extensive metabolizer (EM), diabetes status (history of diabetes mellitus vs. no history of diabetes mellitus), ethnicity (Black vs. Non-Black), age (< 65 and ≥ 65), and gender. The primary statistical method of treatment comparison was a step-down dose response test linear contrast in the ANCOVA. Additionally, a step-up dose response test was performed to evaluate the range of dose efficacy. The sponsor used two-sided statistical tests with a p value of 0.05, unless otherwise stated. For the primary endpoint, covariate interaction in the ITT LOCF population was evaluated at $p < 0.1$. Overall treatment effect was assessed after adjustment for baseline differences and treatment-by-center interaction.

The ITT population consisted of all randomized patients who took at least one dose of double-blind study medication. The Per Protocol (PP) population comprised all randomized patients without major protocol violations.

Secondary Endpoints in Study NEB-302 (Reproduced from Sponsor, page 44)

- Change of average **sitting systolic** blood pressure taken at **trough** drug plasma level (24 ± 2 hours post-previous morning's dose) at end of treatment (Day 84) compared to baseline
- Change of average **sitting systolic and diastolic** blood pressures taken at **peak** drug plasma level (two to three hours post-dose) at end of treatment (Day 84) compared to baseline
- Change of average **supine systolic and diastolic** blood pressures taken at **trough** drug plasma level (24 ± 2 hours post-previous morning's dose) at end of treatment (Day 84)
- Change of average **supine systolic and diastolic** blood pressures taken at **peak** drug plasma level (two to three hours post-dose) at end of treatment (Day 84) compared to baseline
- Change of average **standing systolic and diastolic** blood pressures taken at **trough** drug plasma level (24 ± 2 hours post-previous morning's dose) at end of treatment (Day 84) compared to baseline
- Change of average **standing systolic and diastolic** blood pressures taken at **peak** drug plasma level (two to three hours post-dose) at end of treatment (Day 84) compared to baseline
- Response rates of treatment groups

Secondary Endpoints in Study NEB-302 (Reproduced from Sponsor, page 44) (continued)

- Correlation between plasma levels (at trough and peak) and change of average sitting diastolic blood pressure

A medical reviewer from the _____ reviewed serious adverse events. There was no safety monitoring board.

Results

The demographic and baseline characteristics of the subjects are presented in Table 73.

Table 73. Demographic and Baseline Characteristics of Subjects (Study NEB-302)

Parameter	Placebo n (%)	Nebivolol 1.25 mg n (%)	Nebivolol 2.5 mg n(%)	Nebivolol 5 mg n (%)	Nebivolol 10 mg n (%)	Nebivolol 20 mg n (%)	Nebivolol 30/40 mg n (%)	Total N (%)	p-value[a]
Age (years)									
N	81	83	82	165	166	166	166	909	0.790
Mean (SD)	56.0 (11.6)	55.5 (11.5)	53.4 (12.3)	54.9 (11.8)	55.2 (12.5)	54.1 (11.6)	54.3 (11.6)	54.7 (11.8)	
Median	57.0	56.0	54.0	54.0	54.5	54.0	54.0	54.0	
Range	24.0 to 80.0	28.0 to 84.0	24.0 to 81.0	25.0 to 82.0	23.0 to 83.0	22.0 to 82.0	26.0 to 78.0	22.0 to 84.0	
Age Group									
< 65	64 (79.0)	65 (78.3)	68 (82.9)	132 (80.0)	125 (75.3)	134 (80.7)	128 (77.1)	716 (78.8)	0.827
≥65	17 (21.0)	18 (21.7)	14 (17.1)	33 (20.0)	41 (24.7)	32 (19.3)	38 (22.9)	193 (21.2)	
Gender									
Male	46 (56.8)	46 (55.4)	53 (64.6)	96 (58.2)	93 (56.0)	92 (55.4)	92 (55.4)	518 (57.0)	0.865
Female	35 (43.2)	37 (44.6)	29 (35.4)	69 (41.8)	73 (44.0)	74 (44.6)	74 (44.6)	391 (43.0)	
Race									
Black	11 (13.6)	12 (14.5)	13 (15.9)	23 (13.9)	23 (13.9)	25 (15.1)	25 (15.1)	132 (14.5)	> 0.999
Non-Black	70 (86.4)	71 (85.5)	69 (84.1)	142 (86.1)	143 (86.1)	141 (84.9)	141 (84.9)	777 (85.5)	
Caucasian	61 (75.3)	60 (72.3)	60 (73.2)	120 (72.7)	114 (68.7)	112 (67.5)	113 (68.1)	640 (70.4)	
Asian	0 (0.0)	1 (1.2)	0 (0.0)	1 (0.6)	1 (0.6)	2 (1.2)	1 (0.6)	6 (0.7)	
Hispanic	9 (11.1)	10 (12.0)	9 (11.0)	21 (12.7)	24 (14.5)	25 (15.1)	25 (15.1)	123 (13.5)	
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (2.4)	2 (1.2)	2 (1.2)	8 (0.9)	
Diabetes Status									
Yes	7 (8.6)	9 (10.8)	10 (12.2)	11 (6.7)	17 (10.2)	14 (8.4)	20 (12.0)	88 (9.7)	0.683
No	74 (91.4)	74 (89.2)	72 (87.8)	154 (93.3)	149 (89.8)	152 (91.6)	146 (88.0)	821 (90.3)	
Metabolism									
Poor	4 (4.9)	5 (6.0)	6 (7.3)	10 (6.1)	11 (6.6)	12 (7.2)	11 (6.6)	59 (6.5)	0.995
Extensive	77 (95.1)	78 (94.0)	76 (92.7)	155 (93.9)	155 (93.4)	154 (92.8)	155 (93.4)	850 (93.5)	
BMI (kg/m^2)									
< 30	44 (54.3)	43 (51.8)	45 (54.9)	91 (55.2)	102 (61.4)	101 (60.8)	84 (50.6)	510 (56.1)	0.389
≥ 30	37 (45.7)	40 (48.2)	37 (45.1)	74 (44.8)	64 (38.6)	65 (39.2)	82 (49.4)	399 (43.9)	

(a) From ANOVA with main effect treatment for continuous variables; From a Chi-Square Test for discrete variables
(b) Test of race is black vs. non-black
(c) BMI is the baseline weight in kilograms divided by the square of the baseline height in meters
Cross Reference: Data Listings 1 and 14.3

(Reproduced from Sponsor, NEB-302, Table 1.1.1, pages 131 and 132)

For the ITT nebivolol patients, age, age group, gender, and EM or PM classification were statistically different between the Black and Non-Black populations, as seen in Table 74. Additionally, Blacks in the ITT Nebivolol group had significantly higher sitting and standing diastolic blood pressure at baseline compared to Non-Blacks.

Table 74. Baseline Patient Characteristics by Race (Population: Intent-to-Treat Nebivolol Patients) (NEB-302)

Parameter	Black	Non-Black	p-value[a]
Age (years)			
N	121	707	< 0.001
Mean	50.5 (9.6)	55.3 (12.1)	
Median	48.0	55.0	
Range	26.0 to 77.0	22.0 to 84.0	
Age group			
< 65	107 (88.4)	545 (77.1)	0.005
≥ 65	14 (11.6)	162 (22.9)	
Gender			
Male	57 (47.1)	415 (58.7)	0.017
Female	64 (52.9)	292 (41.3)	
Diabetes Status			
Yes	17 (14.0)	64 (9.1)	0.087
No	104 (86.0)	643 (90.9)	
EM or PM Classification			
Poor	3 (2.5)	52 (7.4)	0.047
Extensive	118 (97.5)	655 (92.6)	
BMI			
N	121	707	0.372
Mean (SD)	28.8 (4.6)	29.2 (3.9)	
Median	29.5	29.4	
Range	17.4 to 37.4	17.8 to 42.2	
Weight (kg)			
N	121	707	0.262
Mean (SD)	84.1 (14.9)	85.8 (15.3)	
Median	82.0	85.9	
Range	51.4 to 122.7	47.3 to 129.5	
Sitting Diastolic Blood Pressure			
N	121	707	< 0.001
Mean (SD)	100.7 (4.0)	99.2 (3.7)	
Median	100.0 (4.0)	99.2 (3.7)	
Range	95.0 to 109.0	77.0 to 110.0	
Standing Diastolic Blood Pressure			
N	121	707	< 0.001
Mean (SD)	101.2 (7.0)	98.7 (5.6)	
Median	100.0	99.0	
Range	83.0 to 116.0	79.0 to 120.0	

(a) From ANOVA with main effect race for continuous variables from a Chi-Square Test for discrete variables
(b) BMI is the baseline weight in kilograms divided by the square of the baseline height in meters
Cross Reference: Data Listings 1 and 14.3

(Adapted from Sponsor, Tables 7.1 and 7.2, pages 137 through 139)

Common co-existing conditions in over 5% of patients were hypercholesterolemia (18.5%), hyperlipidemia (14.9%), hysterectomy (11.6%), seasonal allergies (8.0%), headaches (5.9%), depression (5.4%), cholecystectomy (5.1%), and allergic rhinitis (5.1%).

In the ITT group, 70-81% of patients in each treatment group used concomitant medication during the double-blind treatment period. The most commonly used medications during double-

blind treatment included acetylsalicylic acid (18.2%), acetaminophen/paracetamol (12.9%), multivitamins (11.3%), atorvastatin (7.9%), tocopherol (7.4%),[23] and ibuprofen (5.3%).[24]

Subject disposition is shown in Table 75 below. Four randomized patients never took any study medication, so there were only 909 patients in the ITT population.

Table 75. Patient Disposition (ITT Population) in Study NEB-302

Study Status	Placebo N (%)	Nebivolol 1.25 mg N (%)	Nebivolol 2.5 mg N (%)	Nebivolol 5 mg N (%)	Nebivolol 10 mg N (%)	Nebivolol 20 mg N (%)	Nebivolol 30/40 mg N (5)	Total N (%)
								1573[a]
Single-Blind								1295
Screened								913
ITT	81	83	82	165	166	166	166	909
Completed	67 (82.7)	68 (81.9)	68 (82.9)	148 (89.7)	133 (80.1)	144 (86.7)	149 (89.8)	777 (85.5)
Discontinued								
Total	14 (17.3)	15 (18.1)	14 (17.1)	17 (10.3)	33 (19.9)	22 (13.3)	17 (10.2)	132 (14.5)
Adverse Event	1 (1.2)	3 (3.6)	2 (2.4)	0	7 (4.2)	7 (4.2)	3 (1.8)	23 (2.5)[b,c]
Treatment Failure	4 (4.9)	4 (4.8)	1 (1.2)	3 (1.8)	5 (3.0)	1 (0.6)	1 (0.6)	19 (2.1)
Lost to Follow-Up	2 (2.5)	1 (1.2)	2 (2.4)	4 (2.4)	5 (3.0)	4 (2.4)	5 (3.0)	23 (2.5)
Protocol Deviation	1 (1.2)	3 (3.6)	1 (1.2)	0	1 (0.6)	2 (1.2)	0	8 (0.9)
Withdrew Consent	5 (6.2)	3 (3.6)	5 (6.1)	9 (5.5)	12 (7.2)	7 (4.2)	7 (4.2)	48 (5.3)
Other	1 (1.2)	1 (1.2)	3 (3.7)	1 (0.6)	3 (1.8)	1 (0.6)	1 (0.6)	11 (1.2)

Data Source: Tables 1.8.1 and 1.8.2

[a] Three patients were screened twice. Patient 2111000621 and 2111001882 are the same patient who failed screening twice (wrong study medication dispensed and withdrawn consent, respectively). Patient 2111000330 and 2111001688 are the same patient who failed screening twice (wrong study medication dispensed and discontinued secondary to protocol violation, respectively). Patient 2571002169 and 2571002945 are the same patient who failed screening the first time (withdrawn consent) and qualified the second time. This patient was enrolled as 2571002945. These 3 patients were counted twice in the total number of screened patients.

[b] Two patients withdrawn due to adverse events, 1701000827 (nebivolol 1.25 mg) and 2691000675 (nebivolol 2.5 mg) withdrew during double-blind treatment due to adverse events that started during the placebo run-in. These 2 patients are included as adverse events leading to withdrawal in this table.

[c] Patient 1311000202 (nebivolol 30 mg) is listed on the patient status page as not completing the study due to withdrawn consent. However, on the adverse event page, the patient's AE of dizziness was also listed as leading to withdrawal. To follow the most conservative approach, the patient is listed as discontinuing due to adverse event in this table, whereas, in the database, the patient is listed as discontinued due to withdrawn consent.

(Reproduced from Sponsor, Table 10.1-01, page 59)

The sponsor's analysis of non-compliance (outside ± 10% of randomized dose) gave rates of 2.6% in the placebo group and a range from 1.3% to 4.5% in the nebivolol groups. The highest noncompliance rate was 4.5% in the nebivolol 10 mg group. The p-value, using a Chi-Square Test, was 0.807.

[23] **Tocopherol use was different between groups (placebo: 12.3%; nebivolol 1.25 mg: 2.4%).**

[24] **Ibuprofen use was different between groups (placebo: 6.2%; nebivolol 1.25 mg: 1.2%; nebivolol 5 mg: 8.5%).**

Primary Efficacy Endpoint (NEB-302)

For the primary efficacy endpoint, the sponsor's analysis found that the linear contrasts for nebivolol 1.25, 2.5, 5, 10, and 20 mg in the ITT LOCF Population using the step-down trend test for sitting diastolic blood pressure at trough were statistically significant ($p < 0.001$) from baseline to end of study, as seen in Table 76 below. At the end of study, the ITT OC, PP LOCF, and PP OC results supported the ITT LOCF results. The sponsor studied the nebivolol 30/40 mg group only for safety, so the linear contrast coefficient for this dose was zero for all contrasts.

For all analyses, the antihypertensive effect of all doses was apparent at day 14, except for nebivolol 1.25 mg in the PP LOCF population.

Table 76. LS Mean Change from Baseline to End of Study in Sitting Diastolic Blood Pressure (mm Hg) at Trough and Trend Tests (ITT LOCF) in Study NEB-302

Treatment	N	Baseline Mean	Treatment Mean	Mean Change from Baseline (SD)	LS Mean Change from Baseline (SE)[a]	Step-Down Trend Test p-value[a,b]	Step-Up Trend Test p-value[a,c]
Placebo	81	100.3	97.1	-3.2 (7.7)	-2.9 (1.1)		< 0.001
Nebivolol							
1.25 mg	83	98.9	90.8	-8.0 (7.7)	-8.0 (1.1)	< 0.001	0.073
2.5 mg	82	99.8	91.1	-8.7 (7.7)	-8.5 (1.1)	< 0.001	0.169
5 mg	165	99.6	91.0	-8.6 (8.0)	-8.4 (1.0)	< 0.001	0.130
10 mg	166	99.5	90.2	-9.4 (8.1)	-9.2 (0.9)	< 0.001	0.519
20 mg	166	99.4	89.5	-9.9 (8.7)	-9.8 (0.9)	< 0.001	
30/40 mg	166	99.3	88.0	-11.3 (8.3)	-11.2 (0.9)		

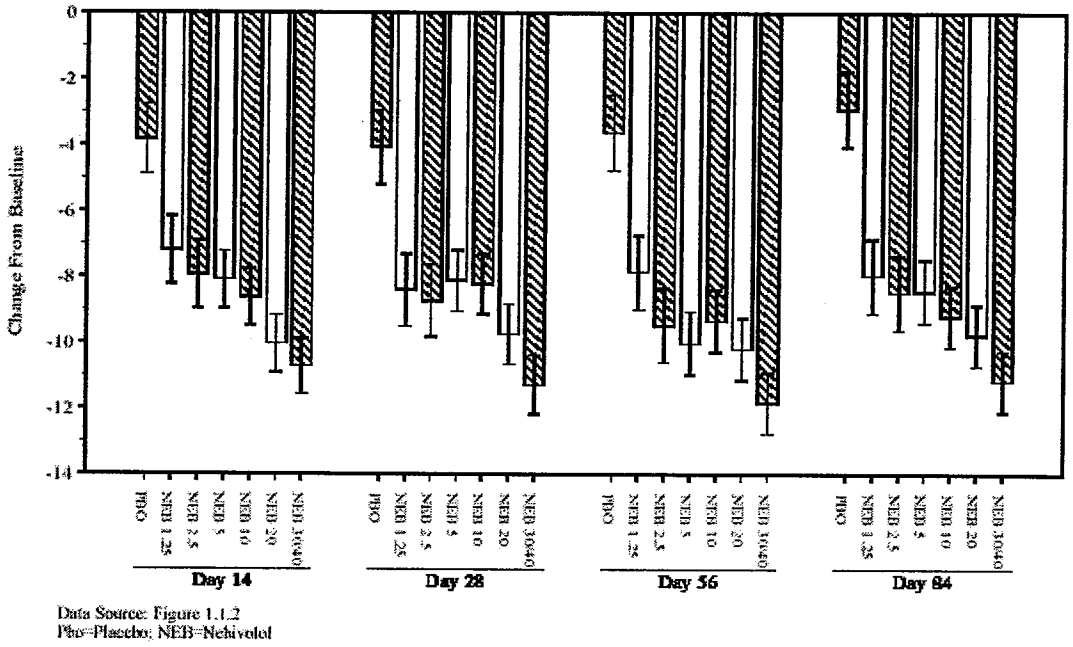
Data Source: Table 2.1.1
[a] From an ANCOVA with factor treatment and covariates baseline blood pressure, metabolism rate, diabetes status, gender, race, and age group
[b] Step-down testing scheme began with treatments placebo through nebivolol 20 mg and proceeded to step down until the trend tests contained only placebo and nebivolol 1.25 mg
[c] Step-up testing scheme began with treatments placebo through nebivolol 20 mg and proceeded to step up until the trend test contained only nebivolol 10 mg and 20 mg

(Reproduced from Sponsor, Table 11.4-02, page 67)

In the step-up trend test for the ITT LOCF population, only the placebo to nebivolol 20 mg contrast was statistically significant.

In Figure 14, the sponsor graphically demonstrates the LS mean changes in the primary efficacy parameter from baseline to end of study.

Figure 14. Bar Graph of LS Mean Change from Baseline to End of Study in Sitting DBP (mm Hg) at Trough by Treatment +/- SE (ITT LOCF) in Study NEB-302



Data Source: Figure 1.1.2
Plac=Placebo; NEB=Nebivolol

(Reproduced from Sponsor, Figure 11.4-02, page 71)

LS Mean Change Difference from Placebo in Primary Efficacy Endpoint (NEB-302)

When the sponsor compared LS mean changes in diastolic blood pressure at trough between nebivolol and placebo, nebivolol was statistically significant at all doses ($p < 0.001$) in the ITT LOCF Population.

Table 77. Differences from Placebo in LS Mean Change from Baseline in Sitting Diastolic Blood Pressure (mm Hg) at Trough (ITT LOCF) (NEB-302)

Treatment Group	N	LS Mean Difference[a,b]	95% CI[a,b]	p-value[a,b]
Nebivolol				
1.25 mg	83	-5.1	(-7.5, -2.6)	< 0.001
2.5 mg	82	-5.6	(-8.0, -3.1)	< 0.001
5 mg	165	-5.5	(-7.7, -3.4)	< 0.001
10 mg	166	-6.3	(-8.4, -4.2)	< 0.001
20 mg	166	-6.9	(-9.0, -4.7)	< 0.001
30/40 mg	166	-8.3	(-10.4, -6.1)	< 0.001

Data Source: Table 2.1.1

[a] **From an ANCOVA with factor, treatment, and covariates baseline blood pressure, metabolism rate, diabetes status, gender, race, and age group.**

[b] **LS mean difference based on pairwise comparison of treatment vs. placebo.**

(Reproduced from Sponsor, Table 11.4-03, page 69)

Sites with GCP Issues (NEB-302)

There were three sites (145, 223, and 133) with GCP issues. Sites 145 and 233 used electronic data capture, but there were inconsistencies between the electronic data, notes, and case report forms. After being informed, the FDA inspected sites 233 and 145. Because of the inconsistencies found at Site 223, Bertek closed down this site. Even when these sites were excluded from the step-down trend test for the ITT LOCF Population at Day 84, all doses of nebivolol from 1.25 to 20 mg were statistically significant, as seen in Table 78 below.

Table 78. LS Mean Change from Baseline to End of Study in Sitting Diastolic Blood Pressure (mm Hg) at Trough and Trend Tests (ITT LOCF Excluding Sites with Potential GCP Issues) for Study NEB-302

Treatment	N	Baseline Mean	Treatment Mean	Mean Change from Baseline (SD)	LS Mean Change from Baseline (SE)[a]	Step-Down Trend Test p-value[a,b]	Step-Up Trend Test p-value[a,c]
Placebo	69	100.5	98.3	-2.1 (7.5)	-2.0 (1.2)	-	< 0.001
Nebivolol							
1.25 mg	74	99.1	91.9	-7.2 (7.3)	-7.2 (1.2)	< 0.001	0.051
2.5 mg	74	99.9	91.9	-7.9 (7.4)	-7.9 (1.2)	< 0.001	0.188
5 mg	144	99.7	91.6	-8.1 (8.0)	-8.1 (1.0)	< 0.001	0.263
10 mg	147	99.6	90.4	-9.1 (8.2)	-9.1 (1.0)	< 0.001	0.994
20 mg	150	99.4	90.3	-9.1 (8.2)	-9.1 (1.0)	< 0.001	
30/40 mg	146	99.3	88.3	-11.0 (8.2)	-11.0 (1.0)		

Data Source: Table 2.1.8

[a] From an ANCOVA with factor treatment and covariates baseline blood pressure, metabolism rate, diabetes status, gender, race, and age group

[b] Step-down testing scheme began with treatments placebo through nebivolol 20 mg and proceeded to step down until the trend tests contained only placebo and nebivolol 1.25 mg

[c] Step-up testing scheme began with treatments placebo through nebivolol 20 mg and proceeded to step up until the trend test contained only nebivolol 10 mg and 20 mg

(Reproduced from Sponsor, Table 11.4-04, page 73)

For the ITT LOCF population, the step-up trend test for sitting diastolic blood pressure at trough from baseline to end of study, excluding sites with potential GCP issues, was significant only for the placebo to nebivolol 20 mg contrast.

Excluding sites with potential GCP issues, the pairwise differences from placebo in LS mean changes from baseline to end of study in the ITT LOCF population were statistically significant ($p < 0.001$) for all doses of nebivolol, as seen in Table 79 below.

Table 79. Differences from Placebo in LS Mean Change from Baseline in Sitting Diastolic Blood Pressure (mm Hg) at Trough (ITT LOCF Excluding Sites with Potential GCP Issues) for Study NEB-302

Treatment Group	N	LS Mean Difference[a,b]	95% CI[a,b]	p-value[a,b]
Nebivolol				
1.25 mg	74	-5.2	(-7.8, -2.6)	< 0.001
2.5 mg	74	-5.9	(-8.5, -3.3)	< 0.001
5 mg	144	-6.0	(-8.3, -3.8)	< 0.001
10 mg	147	-7.1	(-9.3, -4.8)	< 0.001
20 mg	150	-7.1	(-9.3, -4.8)	< 0.001
30/40 mg	146	-9.0	(-11.2, -6.7)	< 0.001

Data Source: Table 2.1.8
[a] From an ANCOVA with factor, treatment, and covariates baseline blood pressure, metabolism rate, diabetes status, gender, race, and age group.
[b] LS mean difference based on pairwise comparison of treatment vs. placebo.

(Reproduced from Sponsor, Table 11.4-05, page 74)

For the primary efficacy endpoint, even the sponsor's "ITT worst case carried forward" analysis demonstrated all nebivolol doses were statistically significantly different in step-down trend testing ($p \leq 0.001$). The worst case carried forward used the worst LS mean between baseline and the last observed value. In this group of patients, however, the step up trend test was significant only for the placebo and nebivolol 1.25 mg linear contrast.

Secondary Efficacy Endpoints (NEB-302)
Analyses of secondary efficacy end-points were performed by the sponsor, as shown in Tables 80 through 85.

Sitting Systolic Blood Pressure at Trough (NEB-302)
In the ITT LOCF Population, the step-down trend test for sitting systolic blood pressure at trough from baseline to the end of study (Day 84) was statistically significant for nebivolol 1.25, 2.5, 5, 10, and 20 mg, as seen in Table 80. In the ITT LOCF Population, these nebivolol doses were statistically significant from Day 14 onward. At Day 84, the ITT OC, PP LOCF, and PP OC analyses supported the ITT LOCF results. At some other study visits, however, nebivolol at particular doses failed to be statistically significant. In the PP LOCF Population on Day 28, for example, nebivolol at doses of 1.25, 2.5, 5, and 10 mg were not statistically significant in lowering sitting systolic blood pressure at trough, although these doses were statistically significant by Day 84. In several cases, depending on the population, lower doses of nebivolol became statistically significant only at the end of treatment.

Table 80. Mean Change from Baseline to End of Study in Sitting Systolic Blood Pressure (mm Hg) at Trough and Trend Tests (ITT LOCF) in Study NEB-302

Treatment	N	Baseline Mean	Treatment Mean	Mean Change from Baseline (SD)	LS Mean Change from Baseline (SE)[a]	Step-Down Trend Test p-value[a,b]	Step-Up Trend Test p-value[a,c]
Placebo	81	154.9	153.5	-1.4 (13.1)	2.2 (1.9)		< 0.001
Nebivolol							
1.25 mg	83	152.2	145.1	-7.1 (12.3)	-4.4 (1.9)	0.002	0.220
2.5 mg	82	150.1	141.5	-8.6 (13.6)	-6.3 (1.9)	< 0.001	0.760
5 mg	165	152.6	143.7	-8.9 (12.4)	-5.9 (1.6)	< 0.001	0.704
10 mg	166	155.8	145.0	-10.7 (14.6)	-7.0 (1.6)	< 0.001	0.690
20 mg	166	151.9	142.7	-9.2 (15.1)	-6.5 (1.6)	< 0.001	
30/40 mg	166	153.1	140.7	-12.4 (15.7)	-9.5 (1.5)		

Data Source: Table 2.2.1
[a] **From an ANCOVA with factor treatment and covariates baseline blood pressure, metabolism rate, diabetes status, gender, race, and age group**
[b] **Step-down testing scheme began with treatments placebo through nebivolol 20 mg and proceeded to step down until the trend tests contained only placebo and nebivolol 12.5 mg**
[c] **Step-up testing scheme began with treatments placebo through nebivolol 20 mg and proceeded to step up until the trend test contained only nebivolol 10 mg and 20 mg**

(Reproduced from Sponsor, Table 11.4-07, page 78)

For the ITT LOCF Population, the step-up trend test for sitting systolic blood pressure at trough from baseline to the end of the study was statistically significant only for the placebo to nebivolol 20 mg contrast. The sponsor suggests these data represent a response differential between placebo and nebivolol. According to the sponsor's interpretation, because the changes in systolic blood pressure at trough were too small, varying effects between nebivolol doses could not be detected.

Differences from Placebo in LS Mean Change from Baseline in Sitting SBP at Trough (NEB-302)

In the ITT LOCF Population using the step-down trend test, the mean change from baseline to end of study in sitting systolic blood pressure at trough was statistically significant for all nebivolol doses (nebivolol 1.25 mg: $p = 0.002$; nebivolol 2.5, 5, 10, and 20 mg: $p < 0.001$). For the ITT LOCF Population, the step-up trend test was significant only for the placebo to nebivolol 20 mg contrast.

Other Secondary Efficacy Endpoints (NEB-302)

In the ITT LOCF Population at trough, all doses of nebivolol resulted in significantly different LS mean changes in diastolic and systolic blood pressure from baseline to end of study. These changes occurred while the patient was sitting, standing, or supine. In general, the ITT OC, PP LOCF, and PP OC analyses supported the ITT LOCF results. At some study visits, however, nebivolol at particular doses in the different study populations was not statistically significant. The summary of results for the ITT LOCF Population at trough from baseline to end of study is shown in Table 81.

Table 81. Summary of Results of the Step-Down Trend Test and LS mean Change in DBP and SBP (mm Hg) at Trough from Baseline to End of Study for Study NEB-302 (ITT LOCF)

	Sitting			Standing			Supine		
	p-value[a,b]	LS Mean[c]	LS Mean Diff	p-value[a,b]	LS Mean[c]	LS Mean Diff	p-value[a,b]	LS Mean[c]	LS Mean Diff
Placebo									
DBP	---	-2.9	---	---	0	---	---	-2.5	---
SBP	---	2.2	---	---	3.8	---	---	0.6	---
Nebivolol 1.25 mg									
DBP	< 0.001	-8.0	-5.1	< 0.001	-4.6	-4.5	0.018	-5.5	-3.0
SBP	0.002	-4.4	-6.6	0.002	-3.0	-6.8	0.011	-4.7	-5.3
Nebivolol 2.5 mg									
DBP	< 0.001	-8.5	-5.6	< 0.001	-6.5	-6.4	< 0.001	-7.6	-5.1
SBP	< 0.001	-6.3	-8.4	< 0.001	-6.3	-10.1	< 0.001	-8.3	-8.9
Nebivolol 5 mg<									
DBP	< 0.001	-8.4	-5.5	< 0.001	-5.2	-5.2	< 0.001	-7.4	-4.9
SBP	< 0.001	-5.9	-8.1	< 0.001	-4.1	-8.0	< 0.001	-7.6	-8.2
Nebivolol 10 mg									
DBP	< 0.001	-9.2	-6.3	< 0.001	-6.6	-6.6	< 0.001	-7.9	-5.4
SBP	< 0.001	-7.0	-9.2	< 0.001	-5.3	-9.1	< 0.001	-7.1	-7.7
Nebivolol 20 mg									
DBP	< 0.001	-9.8	-6.9	< 0.001	-7.4	-7.3	< 0.001	-8.4	-5.9
SBP	< 0.001	-6.5	-8.6	< 0.001	-5.1	-8.9	< 0.001	-7.1	-7.8
Nebivolol 30/40 mg									
DBP	---	-11.2	-8.3	---	-9.1	-9.1	---	-10.1	-7.6
SBP	---	-9.5	-11.7	---	-8.5	-12.4	---	-10.9	-11.5

Data Source: Tables 2.1.1, 2.2.1, 2.5.1, 2.6.1, 2.9.1, and 2.10.1

[a] **p-value from step-down trend test; step-down testing begins with placebo to nebivolol 20 mg and proceeds to step down until the test contains only placebo and nebivolol 1.25 mg**

[b] **From an ANCOVA with factor treatment and covariates baseline blood pressure, EM or PM classification, diabetes status, gender, race, and age group**

[c] **LS mean change in DBP or SBP from baseline to end of study**

(Reproduced from Sponsor, Table 11.4-13, page 91)

At peak, all nebivolol doses statistically significantly lowered systolic and diastolic blood pressure, with the exception of nebivolol 1.25 mg, which did not significantly lower standing and supine systolic blood pressure from baseline to end of study. The summary of results of the step-down trend test and LS mean change in DBP and SBP (mm Hg) at peak from baseline to end of study is shown in Table 82.

Table 82. Summary of Results of the Step-Down Trend Test and LS Mean Change in DBP and SBP (mm Hg) at Peak from Baseline to End of Study for Study NEB-302 (ITT LOCF)

	Sitting			Standing			Supine		
	p-value[a,b]	LS Mean[c]	LS Mean Diff	p-value[a,b]	LS Mean[c]	LS Mean Diff	p-value[a,b]	LS Mean[c]	LS Mean Diff
Placebo									
DBP	---	-5.4	---	---	-3.5	---	---	-4.3	---
SBP	---	-3.1	---	---	-3.4	---	---	-3.8	---
Nebivolol 1.25 mg									
DBP	0.005	-9.1	-3.8	0.014	-6.7	-3.2	0.029	-7.1	-2.8
SBP	0.029	-7.6	-4.5	0.184	-6.2	-2.8	0.120	-7.0	-3.2
Nebivolol 2.5 mg									
DBP	<0.001	-10.1	-4.7	<0.001	-8.1	-4.7	<0.001	-8.7	-4.4
SBP	0.015	-8.1	-5.0	0.028	-8.1	-4.7	0.008	-9.4	-5.6
Nebivolol 5 mg<									
DBP	<0.001	-10.7	-5.4	<0.001	-8.9	-5.4	<0.001	-9.0	-4.7
SBP	<0.001	-9.5	-6.5	<0.001	-10.1	-6.7	<0.001	-9.8	-6.0
Nebivolol 10 mg									
DBP	<0.001	-11.6	-6.2	<0.001	-10.3	-6.9	<0.001	-9.4	-5.1
SBP	<0.001	-11.0	-7.9	<0.001	-10.8	-7.4	<0.001	-11.3	-7.5
Nebivolol 20 mg									
DBP	<0.001	-13.2	-7.8	<0.001	-11.6	-8.1	<0.001	-10.8	-6.5
SBP	<0.001	-13.1	-10.0	<0.001	-11.8	-8.4	<0.001	-11.9	-8.1
Nebivolol 30/40 mg									
DBP	---	-13.9	-8.5	---	-12.8	-9.3	---	-12.0	-7.7
SBP	---	-14.0	-10.9	---	-14.1	-10.7	---	-14.0	-10.2

Data Source: Tables 2.3.1, 2.4.1, 2.7.1, 2.8.1, 2.11.1, and 2.12.1

[a] **p-value from step-down trend test; step-down testing begins with placebo to nebivolol 20 mg and proceeds to step down until the test contains only placebo and nebivolol 1.25 mg**

[b] **From an ANCOVA with factor treatment and covariates baseline blood pressure, EM or PM classification, diabetes status, gender, race, and age group**

[c] **LS mean change in DBP or SBP from baseline to end of study**

(Reproduced from Sponsor, Table 11.4-14, page 92)

Subgroup Analyses

The sponsor performed subgroup analyses (race, age, diabetes status, metabolism of nebivolol, and gender) on the primary and secondary endpoints. For most of these subgroups, there was an unequal distribution of these patients in treatment groups and an inadequate sample size (less than 60 patients needed to have 90% power to detect treatment group differences), so no definitive conclusions could be made.

For sitting diastolic blood pressure at trough, race had a significant effect on treatment group efficacy ($p = 0.023$) using the effects from the full ANCOVA Model. LS Mean differences in Blacks for all nebivolol doses ranged from -3.6 to -9.9 mm Hg. For Non-Blacks, the LS mean difference in placebo-subtracted reductions in sitting diastolic blood pressure at trough from baseline to end of study across nebivolol doses ranged from -4.2 to -8.0 mm Hg, as seen in Table 83. Because only 132 Blacks were enrolled in NEB-302, however, no definitive conclusions could be made.

Table 83. Mean Change from Baseline in Trough Sitting Diastolic Blood Pressure (mm Hg) by Race in Study NEB-302 (Population: Intent-to-Treat Last Observation Carried Forward)

Visit / Treatment	Baseline		Post Baseline		Change From Baseline		LSMean Diff[a,b]	
	Black N Mean (SD)	Non-Black N Mean (SD)	Black N Mean (SD)	Non-Black N Mean (SD)	Black N LSMean[a] (SE)	Non-Black N LSMean[a] (SE)	Black	Non-Black
Day 84								
Placebo	11 101.4 (4.6)	70 100.1 (4.3)	11 102.2 (8.9)	70 96.3 (8.9)	11 -0.2 (2.5)	70 -5.0 (1.2)		
Nebivolol 1.25 mg	12 100.0 (4.1)	71 98.7 (4.5)	12 91.2 (7.0)	71 90.8 (9.0)	12 -10.1 (2.4)	71 -9.3 (1.1)	-9.9	-4.2
Nebivolol 2.5 mg	13 100.9 (2.9)	69 99.6 (3.6)	13 95.8 (5.5)	69 90.2 (8.0)	13 -6.3 (2.3)	69 -10.5 (1.1)	-6.2	-5.5
Nebivolol 5 mg	23 101.1 (4.2)	142 99.3 (3.8)	23 95.3 (10.0)	142 90.3 (8.9)	23 -6.8 (1.8)	142 -10.4 (0.9)	-6.7	-5.3
Nebivolol 10 mg	23 102.5 (4.1)	143 99.1 (3.9)	23 94.6 (10.0)	143 89.4 (8.8)	23 -8.7 (1.8)	143 -11.0 (0.9)	-8.5	-5.9
Nebivolol 20 mg	25 100.3 (3.7)	141 99.2 (3.4)	25 97.6 (8.0)	141 88.0 (8.4)	25 -3.7 (1.7)	141 -12.5 (0.9)	-3.6	-7.5
Nebivolol 30/40 mg	25 99.5 (4.3)	141 99.2 (3.5)	25 90.7 (7.3)	141 87.5 (8.5)	25 -10.0 (1.7)	141 -13.0 (0.9)	-9.8	-8.0
						p-value[c] for test of blacks vs. non-blacks = <0.001		
						p-value[c] for test of equality of linear trends between races = 0.126		

(a) From an ANCOVA with factors treatment, baseline blood pressure, EM or PM classificaton, diabetes status, gender, race, age group, and the treatment by race interaction
(b) LSMean difference of Treatment - Placebo
Cross Reference: Data Listings 1, 10.1.1, 10.2.1, 10.4, and 14.3 and Table 8.8

(Reproduced from Sponsor, Table 5.2.4, page 16)

Although both Blacks and Non-Blacks experienced reductions in all 12 blood pressure parameters from baseline to end of study, the response in Blacks was more variable. Because of the small number of Blacks in each treatment group, however, these results warrant cautious interpretation.

Change in trough sitting diastolic blood pressure from baseline to Day 84 by race is shown in Table 84 and Table 85. No doses of nebivolol were statistically significant by step-down trend testing for this parameter, while all doses were statistically significant for Non-Blacks.

Table 84. Mean Change From Baseline in Trough Sitting Diastolic Blood Pressure (mm Hg) by Treatment and Subgroup at Day 84 (Population: Intent-to-Treat Last Observation Carried Forward) for Study NEB-302

Subgroup	N	Baseline Mean	Treatment Mean	Change From Baseline						
				Mean (SD)	LSMean (SE)	Step-Down p-value[a,b]	LSMean Diff[a,c]	95% C.I.[a,c]	p-value[a,c]	Step-Up p-value[a,b]
Race										
Black										
Placebo	11	101.4	102.2	0.8 (6.8)	-0.5 (3.6)					0.396
Nebivolol 1.25 mg	12	100.0	91.2	-8.8 (6.5)	-10.5 (3.6)	0.004[NS]	-10.0	(-16.8, -3.2)	0.004[NS]	0.140[NS]
Nebivolol 2.5 mg	13	100.9	95.8	-5.2 (5.5)	-6.2 (3.4)	0.101[NS]	-5.7	(-12.5, 1.1)	0.101[NS]	0.711[NS]
Nebivolol 5 mg	23	101.1	95.3	-5.8 (9.0)	-6.7 (2.9)	0.146[NS]	-6.2	(-12.3, -0.2)	0.043[NS]	0.321[NS]
Nebivolol 10 mg	23	102.5	94.6	-8.0 (9.6)	-8.9 (3.1)	0.055[NS]	-8.4	(-14.4, -2.5)	0.006[NS]	0.060[NS]
Nebivolol 20 mg	25	100.3	97.6	-2.6 (8.5)	-4.3 (3.0)	0.396	-3.8	(-9.7, 2.0)	0.199[NS]	
Nebivolol 30/40 mg	25	99.5	90.7	-8.8 (7.7)	-10.6 (2.9)	NA	-10.1	(-16.1, -4.1)	0.001[NS]	

(a) From an ANCOVA with factor treatment and covariates baseline blood pressure, EM or PM classification, diabetes status, gender, race, BMI group, and age group, with the covariate under analysis removed from the model

(b) Step-down testing scheme begins with treatments placebo through Nebivolol 20 mg and proceeds to step-down until the trend test contains only placebo and Nebivolol 1.25 mg; Step-up testing scheme begins with treatments placebo through Nebivolol 20mg and proceeds to step-up until the trend test contains only the 10 and 20 mg Nebivolol doses

(c) Based on pairwise comparison of Treatment vs. Placebo

(d) BMI is the baseline weight in kilograms divided by the square of the baseline height in meters

(*) P-value for test of equality of linear trends between subgroup levels significant at the 0.05 level; from an ANCOVA with factor treatment and covariates baseline blood pressure, EM or PM classification, diabetes status, gender, race, BMI group, and age group and the treatment by covariate under analysis interaction

NS: P-values associated with the 30/40 mg treatment group should not be used due to dependency on 20 mg result; P-values associated with lower doses should not be used in the context of step-down trend testing; P-values associated with higher doses should not be used in the context of step-up trend testing (see analysis plan for explanation)

Cross Reference: Data Listings 1, 10.1.1, 10.2.1, 10.4, and 14.3 and Appendix Table 8.1

(Reproduced from Sponsor, Table 2.16, page 678)

Table 85. Mean Change From Baseline in Trough Sitting Diastolic Blood Pressure (mm Hg) by Treatment and Subgroup at Day 84 (Population: Intent-to-Treat Last Observation Carried Forward) for Study NEB-302

Subgroup	N	Baseline Mean	Treatment Mean	Change From Baseline						
				Mean (SD)	LSMean (SE)	Step-Down p-value[a,b]	LSMean Diff[a,c]	95% C.I.[a,c]	p-value[a,c]	Step-Up p-value[a,b]
Race										
Non-Black										
Placebo	70	100.1	96.3	-3.8 (7.6)	-5.1 (1.2)					<0.001
Nebivolol 1.25 mg	71	98.7	90.8	-7.9 (7.9)	-9.3 (1.2)	0.002	-4.2	(-6.9, -1.6)	0.002	0.010
Nebivolol 2.5 mg	69	99.6	90.2	-9.3 (7.9)	-10.5 (1.2)	<0.001	-5.4	(-8.1, -2.8)	<0.001	0.083
Nebivolol 5 mg	142	99.3	90.3	-9.0 (7.8)	-10.4 (1.0)	<0.001	-5.3	(-7.6, -3.0)	<0.001	0.030[NS]
Nebivolol 10 mg	143	99.1	89.4	-9.6 (7.9)	-11.0 (0.9)	<0.001	-5.9	(-8.1, -3.6)	<0.001	0.111[NS]
Nebivolol 20 mg	141	99.2	88.0	-11.2 (8.1)	-12.5 (1.0)	<0.001	-7.4	(-9.7, -5.1)	<0.001	
Nebivolol 30/40 mg	141	99.2	87.5	-11.7 (8.3)	-13.1 (0.9)	NA	-8.0	(-10.3, -5.7)	<0.001	

(a) From an ANCOVA with factor treatment and covariates baseline blood pressure, EM or PM classification, diabetes status, gender, race, BMI group, and age group, with the covariate under analysis removed from the model

(b) Step-down testing scheme begins with treatments placebo through Nebivolol 20 mg and proceeds to step-down until the trend test contains only placebo and Nebivolol 1.25 mg; Step-up testing scheme begins with treatments placebo through Nebivolol 20mg and proceeds to step-up until the trend test contains only the 10 and 20 mg Nebivolol doses

(c) Based on pairwise comparison of Treatment vs. Placebo

(d) BMI is the baseline weight in kilograms divided by the square of the baseline height in meters

(*) P-value for test of equality of linear trends between subgroup levels significant at the 0.05 level; from an ANCOVA with factor treatment and covariates baseline blood pressure, EM or PM classification, diabetes status, gender, race, BMI group, and age group and the treatment by covariate under analysis interaction

NS: P-values associated with the 30/40 mg treatment group should not be used due to dependency on 20 mg result; P-values associated with lower doses should not be used in the context of step-down trend testing; P-values associated with higher doses should not be used in the context of step-up trend testing (see analysis plan for explanation)

Cross Reference: Data Listings 1, 10.1.1, 10.2.1, 10.4, and 14.3 and Appendix Table 8.1

(Reproduced from Sponsor, Table 2.16, page 679)

The summary of change in trough sitting diastolic blood pressure from baseline to end of study by subgroup is shown in Table 86 and Table 87 below.

Table 86. Summary of Change in Trough Sitting DBP (mm Hg) from Baseline to End of Study by Subgroup (Race, Age and Gender; ITT LOCF) for Study NEB-302

	Race						Age (Years)						Gender					
	Black			Non-Black			<65			≥65			Male			Female		
	N	LS Mean[a] (SE)	LS Mean Diff[b,c]	N	LS Mean[a] (SE)	LS Mean Diff[b,c]	N	LS Mean[a] (SE)	LS Mean Diff[b,c]	N	LS Mean[a] (SE)	LS Mean Diff[b,c]	N	LS Mean[a] (SE)	LS Mean Diff[b,c]	N	LS Mean[a] (SE)	LS Mean Diff[b,c]
Placebo	11	-0.5 (3.6)	—	70	-5.1 (1.2)	—	64	-2.3 (1.3)	—	17	-6.0 (2.3)	—	46	-2.2 (1.5)	—	35	-4.2 (1.8)	—
Nebivolol 1.25mg	12	-10.5 (3.6)	-10.0	71	-9.3 (1.2)	-4.2	65	-8.1 (1.3)	-5.8	18	-7.9 (2.2)	-1.9	46	-7.1 (1.5)	-4.9	37	-9.2 (1.7)	-5.0
2.5mg	13	-6.2 (3.4)	-5.7	69	-10.5 (1.2)	-5.4	68	-8.3 (1.2)	-6.1	14	-9.5 (2.4)	-3.6	53	-7.9 (1.4)	-5.7	29	-9.2 (1.8)	-5.0
5mg	23	-6.7 (2.9)	-6.2	142	-10.4 (1.0)	-5.3	132	-8.3 (1.1)	-6.0	33	-9.4 (1.9)	-3.4	96	-8.1 (1.3)	-5.8	69	-8.9 (1.5)	-4.7
10mg	23	-8.9 (3.1)	-8.4	143	-11.0 (0.9)	-5.9	125	-9.2 (1.1)	-6.9	41	-9.6 (1.8)	-3.7	93	-8.4 (1.3)	-6.2	73	-10.5 (1.4)	-6.4
20mg	25	-4.3 (3.0)	-3.8	141	-12.5 (1.0)	-7.4	134	-9.6 (1.0)	-7.3	32	-10.8 (2.0)	-4.8	92	-9.3 (1.3)	-7.1	74	-10.6 (1.4)	-6.5
30/40mg	25	-10.6 (2.9)	-10.1	141	-13.1 (0.9)	-8.0	128	-11.5 (1.1)	-9.2	38	-10.6 (1.8)	-4.6	92	-11.9 (1.2)	-9.7	74	-10.6 (1.4)	-6.5

Data Source: Table 2.16
[a] LS mean change in DBP from baseline to end of study
[b] From an ANCOVA with factor treatment and covariates baseline blood pressure, EM or PM classification, diabetes status, gender, race and age group with covariate from the analysis removed from the model
[c] Based on pairwise comparison of treatment vs. placebo

(Reproduced from Sponsor, Table 11.4-17, page 98)

Table 87. Summary of Change in Trough Sitting DBP (mm Hg) from Baseline to End of Study by Subgroup (BMI, Diabetes Status and EM/PM Classification; ITT LOCF) for Study NEB-302

	BMI (kg/m²)						Diabetes Status						PM or EM Classification					
	<30			≥30			Yes			No			PM			EM		
	N	LS Mean[a] (SE)	LS Mean Diff[b,c]	N	LS Mean[a] (SE)	LS Mean Diff[b,c]	N	LS Mean[a] (SE)	LS Mean Diff[b,c]	N	LS Mean[a] (SE)	LS Mean Diff[b,c]	N	LS Mean[a] (SE)	LS Mean Diff[b,c]	N	LS Mean[a] (SE)	LS Mean Diff[b,c]
Placebo	44	-5.0 (1.6)	—	37	-0.4 (1.7)	—	7	-4.9 (4.2)	—	74	-2.1 (1.1)	—	4	-2.7 (6.5)	—	77	-2.1 (1.0)	—
Nebivolol 1.25mg	43	-9.8 (1.6)	-4.9	40	-5.8 (1.6)	-5.4	9	-9.3 (4.1)	-4.4	74	-7.1 (1.1)	-5.1	5	-8.9 (6.2)	-6.2	78	-7.1 (1.0)	-5.1
2.5mg	45	-9.6 (1.5)	-4.6	37	-7.0 (1.7)	-6.6	10	-14.7 (3.7)	-9.8	72	-7.0 (1.1)	-5.0	6	-12.8 (5.3)	-10.1	76	-7.2 (1.0)	-5.2
5mg	91	-10.7 (1.3)	-5.7	74	-5.6 (1.5)	-5.2	11	-6.9 (4.0)	-2.0	154	-7.8 (0.9)	-5.8	10	-10.8 (5.2)	-8.1	155	-7.4 (0.8)	-5.3
10mg	102	-11.0 (1.2)	-6.0	64	-6.7 (1.5)	-6.3	17	-10.7 (3.6)	-5.9	149	-8.4 (0.9)	-6.3	11	-13.6 (5.4)	-10.9	155	-7.9 (0.8)	-5.9
20mg	101	-11.4 (1.2)	-6.4	65	-7.7 (1.5)	-7.3	14	-13.2 (3.8)	-8.4	152	-8.8 (0.9)	-6.7	12	-10.0 (5.2)	-7.3	154	-8.8 (0.8)	-6.8
30/40mg	84	-13.8 (1.3)	-8.8	82	-8.1 (1.4)	-7.7	20	-10.9 (3.2)	-6.0	146	-10.7 (0.9)	-8.7	11	-11.0 (4.7)	-8.3	155	-10.3 (0.8)	-8.3

Data Source: Table 2.16
[a] LS mean change in DBP from baseline to end of study
[b] From an ANCOVA with factor treatment and covariates baseline blood pressure, EM or PM classification, diabetes status, gender, race and age group with covariate from the analysis removed from the model.
[c] Based on pairwise comparison of treatment vs placebo

(Reproduced from Sponsor, Table 11.4-18, page 99)

The mean change in sitting diastolic blood pressure from baseline to end of study by race demonstrated that Non-Blacks had a better blood pressure response than Blacks. Because there

were fewer than 60 blacks per treatment group, however, no definitive conclusions can be made. In general, Blacks had higher baseline mean diastolic blood pressures than Non-Blacks. Table 88 describes the mean change in trough sitting diastolic blood pressure by race.

Table 88. Mean Change from Baseline in Trough Sitting Diastolic Blood Pressure (mm Hg) at Day 84 (Population; Intent-to-Treat Last Observation Carried Forward Nebivolol Patients[a]) (NEB-302)

Parameter	Blacks				Non-Blacks			
	n (%)	Baseline Mean	Day 84 Mean	Change Mean	n (%)	Baseline Mean	Day 84 Mean	Change Mean
Age Group								
< 65	107 (88.4)	101.0	94.6	-6.4	545 (77.1)	99.6	89.3	-10.3
≥ 65	14 (11.6)	98.4	92.1	-6.4	162 (22.9)	97.8	88.6	-9.2
Gender								
Male	57 (47.1)	101.6	94.0	-7.6	415 (58.7)	99.5	89.7	-9.8
Female	64 (52.9)	100.0	94.6	-5.4	292 (41.3)	98.7	88.4	-10.3
Diabetes Status								
Yes	17 (14.0)	100.6	93.5	-7.1	64 (9.1)	98.8	87.3	-11.5
No	104 (86.0)	100.8	94.5	-6.3	643 (90.9)	99.2	89.3	-9.9
EM or PM Classification								
Poor	3 (2.5)	99.7	92.0	-7.7	52 (7.4)	99.3	87.3	-11.9
Extensive	118 (97.5)	100.8	94.4	-6.4	655 (92.6)	99.2	89.3	-9.9
BMI[b] (kg/m^2)								
< 30	65 (53.7)	101.1	94.1	-7.0	401 (56.7)	98.8	88.6	-10.2
≥ 30	56 (46.3)	100.3	94.6	-5.7	306 (43.3)	99.7	89.9	-9.8

(a) Only Nebivolol treatments are pooled for this analysis
(b) BMI is the baseline weight in kilograms divided by the square of the baseline height in meters

(Reproduced from Sponsor, Table 7.5, page 142)

Interaction by Site (NEB-302)

For all primary and secondary efficacy endpoints, the sponsor found no significant interaction by site.

Response Rates (NEB-302)

The sponsor defined a responder as "a patient whose average sitting diastolic blood pressure at trough at end of study was either < 90 mm Hg or had decreased by ≥ 10 mm Hg from baseline."[25] In general, responder rates plateaued by Days 28 -56 and increased by dose, as seen in Table 90 and Table 90 below. For all nebivolol doses, the response rate was statistically significantly better than placebo. The ITT OC, PP OC, and PP LOCF analyses supported the ITT LOCF results, except nebivolol 1.25 mg was not significantly better than placebo.

Table 89. Responder[a] Rates by Treatment. Evaluation of Possible Predictors of Responders (ITT LOCF) (NEB-302)

Treatment	Total	Responder n (%)[b]	p-value[c]
Placebo	81	20 (24.7)	
Nebivolol 1.25 mg	83	38 (45.8)	0.008
Nebivolol 2.5 mg	82	41 (50.0)	0.001
Nebivolol 5 mg	165	83 (50.3)	< 0.001
Nebivolol 10 mg	166	89 (53.6)	< 0.001
Nebivolol 20 mg	166	99 (59.6)	< 0.001

[25]Sponsor, Study NEB-302, page 100.

Nebivolol 30/40 mg	166	107 (64.5)	N/A

[a] A subject is a responder if their average trough sitting diastolic blood pressure < 90 mm Hg at end of study or has decreased by ≥ 10 mm Hg from baseline
[b] Percentage is the percentage of responders within that category
[c] Based on Wald Chi-Square Test for trend from logistic regression with factor treatment and covariates baseline blood pressure, EM or PM classification, diabetes status, gender, race, and age group; Step-down testing scheme begins with treatments placebo through Nebivolol 20 mg and proceeds to step-down until the trend test contains only placebo and nebivolol 1.25 mg
NS: P-values should not be used in the context of step-down trend testing (see analysis plan for explanation)

(Reproduced from Sponsor, Study NEB-302, Table 2.13.1, page 648)

Table 90. Responder[a] Rates by Treatment and Visit in Study NEB-302

Visit	Placebo n(%)[b]	Nebivolol 1.25 mg n (%)[b]	Nebivolol 2.5 mg n (%)[b]	Nebivolol 5 mg n (%)[b]	Nebivolol 10 mg n (%)[b]	Nebivolol 20 mg n (%)[b]	Nebivolol 30/40 mg n (%)[b]	Total n (%)[b]
Day 14	22 (27.2)	39 (47.0)	33 (40.2)	94 (57.0)	89 (53.6)	99 (59.6)	111 (66.9)	487 (53.6)
Day 28	28 (34.6)	52 (62.7)	42 (51.2)	81 (49.1)	93 (56.0)	96 (57.8)	115 (69.3)	507 (55.8)
Day 56	21 (25.9)	44 (53.0)	44 (53.7)	95 (57.6)	100 (60.2)	102 (61.4)	108 (65.1)	514 (56.5)
Day 84	20 (24.7)	38 (45.8)	41 (50.0)	83 (50.3)	89 (53.6)	99 (59.6)	107 (64.5)	477 (52.5)

[a] A subject is a responder if their average trough sitting diastolic blood pressure < 90 mm hg at endpoint of interest or has decreased by ≥ 10 mm hg from baseline
[b] Percentage is the percentage of responders within that category
Cross Reference: Data Listings 10.1.1, 10.2.1, and 10.4

(Reproduced from Sponsor, Table 2.13.5, page 652)

Non-Blacks had a statistically significantly greater increase in response rate compared with Blacks, as seen in Table 91 below.

Table 91. Responder[a] Rates by Treatment and Baseline Characteristic at Day 84 (End of Study) (ITT LOCF) (NEB-302)

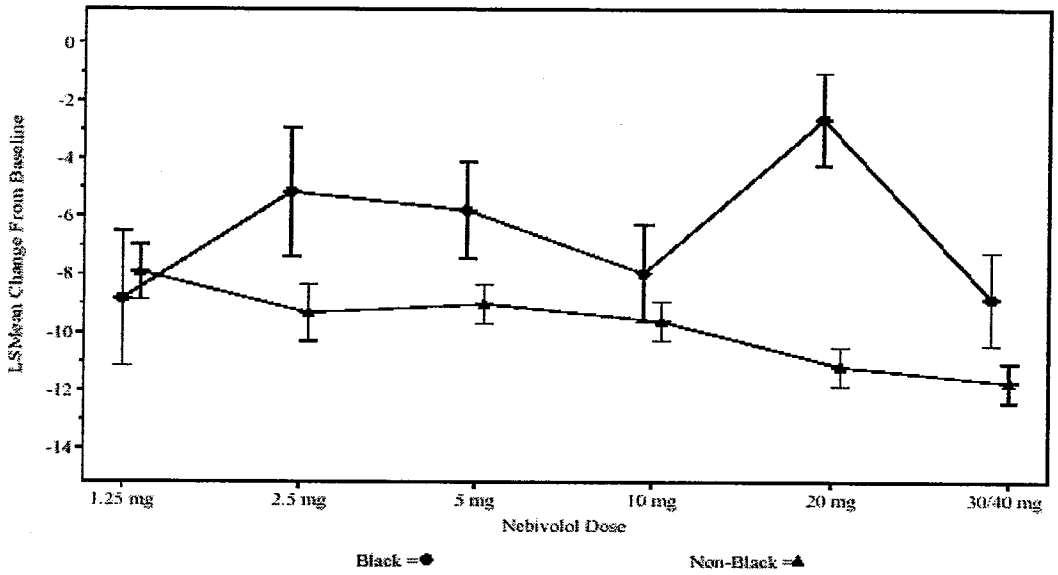
Characteristic Subgroup	Placebo n (%)[b]	Nebivolol 1.25 mg n (%)[b]	Nebivolol 2.5 mg n (%)[b]	Nebivolol 5 mg n (%)[b]	Nebivolol 10 mg n (%)[b]	Nebivolol 20 mg n (%)[b]	Nebivolol 30/40 mg n (%)[b]	Total n (%)[b]	Subgroup p-value[c]
Age									
< 65	14 (21.9)	29 (44.6)	35 (51.5)	69 (52.3)	66 (52.8)	78 (58.2)	86 (67.2)	377 (52.7)	0.216
≥ 65	6 (35.3)	9 (50.0)	6 (42.9)	14 (42.4)	23 (56.1)	21 (65.6)	21 (55.3)	100 (51.8)	
Gender									
Male	11 (23.9)	17 (37.0)	26 (49.1)	46 (47.9)	48 (51.6)	56 (60.9)	66 (71.7)	270 (52.1)	0.687
Female	9 (25.7)	21 (56.8)	15 (51.7)	37 (53.6)	41 (56.2)	43 (58.1)	41 (55.4)	207 (52.9)	
Race									
Black	1 (9.1)	6 (50.0)	4 (30.8)	7 (30.4)	10 (43.5)	6 (24.0)	12 (48.0)	46 (34.8)	<0.001
Non-Black	19 (27.1)	32 (45.1)	37 (53.6)	76 (53.5)	79 (55.2)	93 (66.0)	95 (67.4)	431 (55.5)	
Diabetes Status									
Yes	2 (28.6)	7 (77.8)	7 (70.0)	5 (45.5)	9 (52.9)	10 (71.4)	10 (50.0)	50 (56.8)	0.310
No	18 (24.3)	31 (41.9)	34 (47.2)	78 (50.6)	80 (53.7)	89 (58.6)	97 (66.4)	427 (52.0)	
EM or PM Classification									
Poor	0 (0.0)	1 (20.0)	4 (66.7)	6 (60.0)	9 (81.8)	8 (66.7)	7 (63.6)	35 (59.3)	0.477
Extensive	20 (26.0)	37 (47.4)	37 (48.7)	77 (49.7)	80 (51.6)	91 (59.1)	100 (64.5)	442 (52.0)	

(a) A subject is a responder if their average trough sitting diastolic blood pressure < 90 mmHg at end of study or has decreased by ≥ 10 mmHg from baseline
(b) Percentage is the percentage of responders within that category
(c) Test of difference between subgroups based on Wald Chi-Square Test from logistic regression with factor treatment and covariates baseline blood pressure, EM or PM classification, diabetes status, gender, race, and age group
Cross Reference: Data Listings 2, 10.1.1, 10.2.1, 10.4, and 14.3

(Reproduced from Sponsor, Table 2.13.9, page 656)

The sponsor graphically demonstrates the change in LS mean by race from baseline in trough sitting diastolic blood pressure in Figure 15 below.

Figure 15. LS Mean Change from Baseline in Trough Sitting Diastolic Blood Pressure +/- S.E. by Race (Population: Intent-to-Treat Last Observation Carried Forward Nebivolol Patients) (NEB-302)



(Reproduced from Sponsor, Figure 3.2, page 238)

Correlation of Peak and Trough Plasma Nebivolol Levels (NEB-302)

For sitting diastolic blood pressure reductions at Day 84, the sponsor's analysis showed a statistically significant correlation with log transformed plasma concentrations of *d,l*-nebivolol, *d*-nebivolol, *l*-nebivolol and nebivolol glucuronides at peak and trough, with the exception of nebivolol glucuronides at trough. The correlation is shown in Table 92 below and Figure 16.

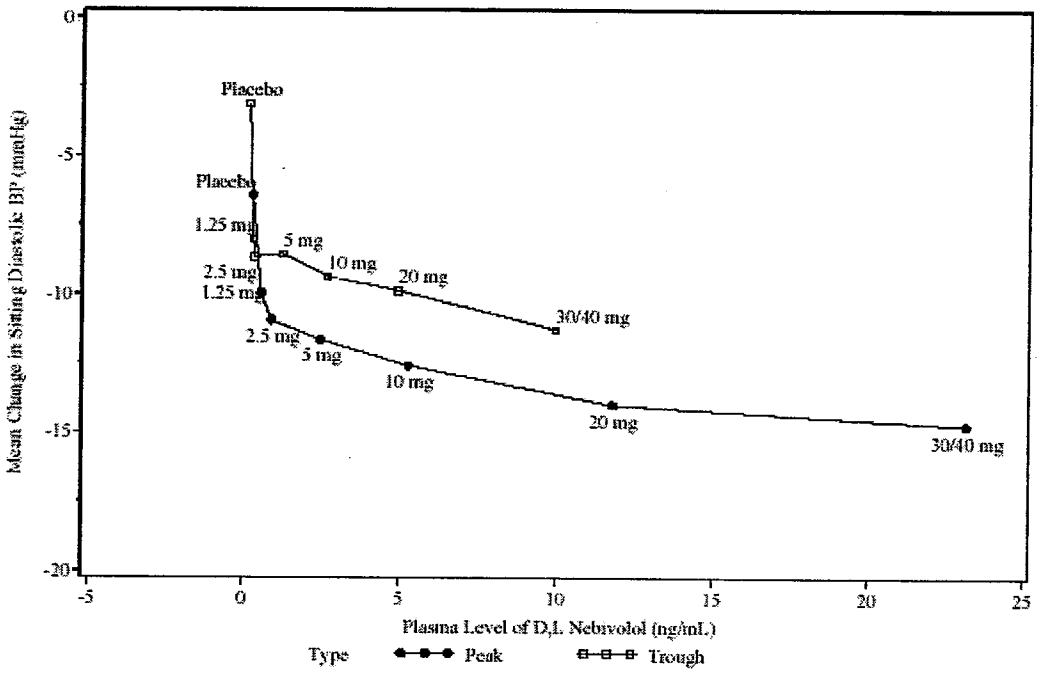
Table 92. Correlation of the Change in Sitting DBP from Baseline to the End of Study with Mean Plasma Concentration at Peak and Trough (ITT LOCF) for Study NEB-302

	N	Mean BP reduction mm Hg	Mean plasma concentration, ng/mL	Correlation	P-value[a]
***d,l*-Nebivolol**					
Peak	756	-13.1	2.4	-0.157	< 0.001
Trough	691	-10.1	0.5	-0.120	0.002
***d*-Nebivolol**					
Peak	745	-13.1	0.9	-0.168	< 0.001
Trough	612	-10.2	0.2	-0.089	0.028
***l*-Nebivolol**					
Peak	757	-13.1	1.5	-0.153	< 0.001
Trough	689	-10.1	0.3	-0.120	0.002
Nebivolol Glucuronides					
Peak	750	-13.2	47.3	-0.168	< 0.001
Trough	549	-10.6	9.2	-0.058	0.177

Data Source Tables 2.14, 2.14.2, 2.14.3, 2.14.4, 2.14.5, 2.14.6, 2.14.13, and 2.14.15
[a] From Pearson's Correlation
Bold is Reviewer's emphasis

(Reproduced from Sponsor, Study NEB-302, Table 11.4-19, page 102)

Figure 16. Correlation of Reduction in Sitting DBP with Mean Plasma *D, L* Nebivolol level at Peak and Trough at Day 84 (ITT LOCF) (NEB-302)



(Reproduced from Sponsor, Study NEB-302, Figure 1.13.32, page 204)

For reductions in sitting heart rate at Day 84, the sponsor's analysis showed a statistically significant correlation with log transformed plasma concentrations of *d,l*-nebivolol, *d*-nebivolol, *l*-nebivolol and nebivolol glucuronides at peak and trough. Table 93 and Figure 17 show the correlation between plasma concentration of nebivolol and heart rate reduction.

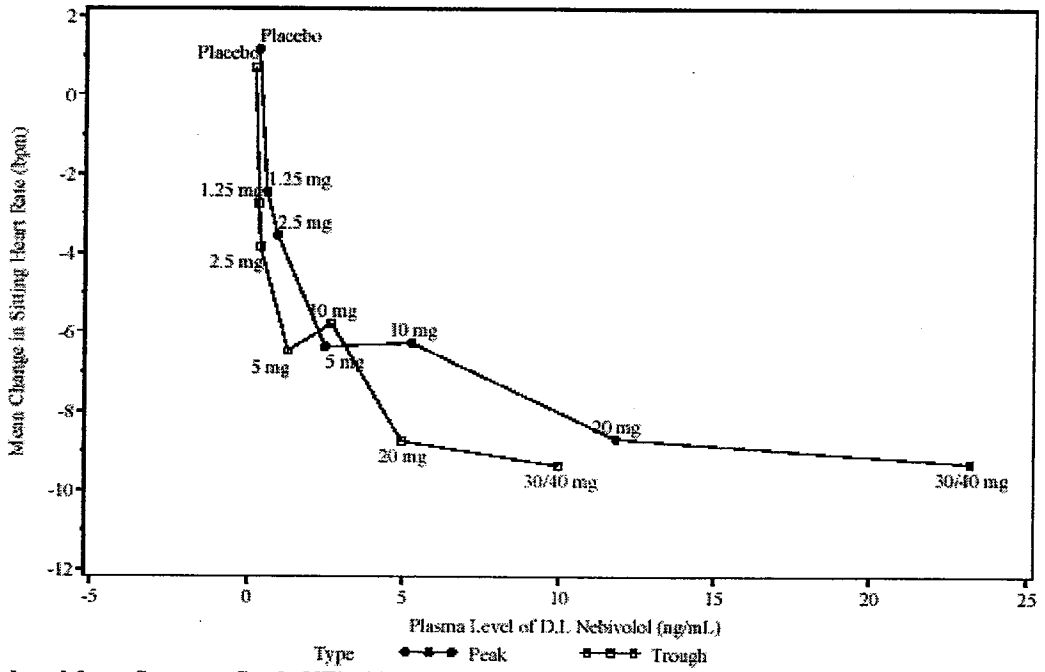
Table 93. Correlation of the Change in Sitting Heart Rate from Baseline to the End of Study with Mean Plasma Concentration at Peak and Trough (ITT LOCF) (NEB-302)

	N	Mean BP reduction mm Hg	Mean plasma concentration, ng/mL	Correlation	P-value[a]
***d,l*-Nebivolol**					
Peak	756	-7.0	2.4	-0.249	< 0.001
Trough	691	-7.4	0.5	-0.163	< 0.001
***d*-Nebivolol**					
Peak	745	-7.1	0.9	-0.247	< 0.001
Trough	612	-7.8	0.2	-0.135	< 0.001
***l*-Nebivolol**					
Peak	757	-7.0	1.5	-0.249	< 0.001
Trough	689	-7.4	0.3	-0.146	< 0.001
Nebivolol Glucuronides					
Peak	750	-7.1	47.3	-0.264	< 0.001
Trough	549	-8.0	9.2	-0.116	0.007

Data Source Tables 2.14.7, 2.14.8, 2.14.9, 2.14.10, 2.14.11, 2.14.12, 2.14.17, and 2.14.19
[a] From Pearson's Correlation

(Reproduced from Sponsor, Study NEB-302, Table 11.4-20, page 103)

Figure 17. Correlation of Reduction in Sitting HR with Mean Plasma *D, L* Nebivolol Level at Peak and Trough at Day 84 (ITT LOCF) (NEB-302)



(Reproduced from Sponsor, Study NEB-302, figure 1.13.40), page 212)

The sponsor suggests there was a plateau in pharmacodynamic effects of nebivolol at doses of 5 to 10 mg at peak and trough. I believe, however, Figure 16 and Figure 17 suggest the plateau occurs either between 10 and 20 mg or between 20 and 30/40 mg for sitting diastolic blood pressure and between 20 and 30/40 mg for sitting heart rate. From the clinical data, this reviewer continues to note further dose-dependent reductions in both diastolic blood pressure and heart rate from baseline to end of study at nebivolol doses of 20 and 30/40 mg.

Although the sponsor attempted to describe the effect of *d*- and *l*-nebivolol on reduction of diastolic blood pressure and heart rate in hypertensive patients in NEB-302, Dr. Mishina found the Emax model proposed by the sponsor to be unacceptable. The Emax model used an "unreasonably low EC50 value of 0.068 ng/mL" to reflect the effect of nebivolol on diastolic blood pressure. According to Dr. Mishina, this low EC50 value was "220 fold higher than the in *vitro* affinity of nebivolol to β_1-adrenoceptors in human myocardium (Ki 5-15 ng/mL)." In NEB-302, the average *d*-nebivolol plasma concentration associated with diastolic blood pressure reduction was 6 ng/mL, similar in magnitude to the Ki value. For heart rate reduction, the sponsor used an EC50 value of 0.0017 ng/mL. For both diastolic blood pressure and heart rate reduction, the "EC50 values estimated by the sponsor [did] not reflect the physiologic parameters for ß-adrenoceptor activity of nebivolol" (Mishina E, Executive Summary, 2005, Clinical Pharmacology Review, Cardio-Renal Division, NDA 21,742). As such, Dr. Mishina found the PK/PD population models proposed by the sponsor to be unacceptable.

Trough to Peak Ratios (NEB-302)

The overall placebo-subtracted trough to peak ratio for sitting diastolic blood pressure reduction from baseline to the end of treatment was 0.9, suggesting that once daily dosing was appropriate. The trough to peak ratios for the individual doses are shown in Table 94.

Table 94. Placebo Subtracted Trough to Peak Ratio for Change from Baseline in Sitting Diastolic Blood Pressure at Day 84. (Population: Intent-to-Treat Last Observation Carried Forward) (NEB-302)

Treatment	N	Trough Mean	Peak Mean	Active - Placebo		
				Trough Mean	Peak Mean	Ratio
Placebo	81	-3.2	-6.4			
Nebivolol 1.25 mg	83	-8.0	-10.0	-4.9	-3.5	1.4
Nebivolol 2.5 mg	82	-8.7	-11.0	-5.5	-4.5	1.2
Nebivolol 5 mg	165	-8.6	-11.7	-5.4	-5.2	1.0
Nebivolol 10 mg	166	-9.4	-12.6	-6.2	-6.2	1.0
Nebivolol 20 mg	166	-9.9	-14.0	-6.7	-7.6	0.9
Nebivolol 30/40 mg	166	-11.3	-14.8	-8.1	-8.3	1.0
Cross Reference: Data Listings 10.1.1, 10.2.1, 10.3.1, and 10.4						

(Reproduced from Sponsor, Table 2.15, page 677)

Overall, 777/909 (85.5%) patients completed Study NEB-302. Twenty-three (2.5%) of patients were lost to follow-up. There were no deaths. According to the sponsor's analysis, protocol deviations occurred in 32/81 (39.5%) of placebo and 242/828 (29.2%) of nebivolol patients. The sponsor indicated the most common major protocol violations were clinic visits (15.2%), trough blood pressure measurement (10.7%), and/or peak blood pressure measurements (9.1%).

Summary (NEB-302)

In the ITT LOCF Population, nebivolol 1.25, 2.5, 5, 10, and 20 mg had statistically significant effects on the primary endpoint. The ITT OC, PP LOCF, and PP OC results supported the ITT LOCF results. By step-up trend testing in the ITT LOCF Population, only the placebo to nebivolol 20 mg contrast was statistically significant for the primary endpoint.

For secondary endpoints at trough, nebivolol 1.25 mg through 20 mg was statistically significant for the ITT LOCF Population. At peak, all doses of nebivolol significantly lowered blood pressure, with the exception of nebivolol 1.25 mg, which did not significantly lower standing and supine systolic blood pressure from baseline to end of study. For sitting systolic blood pressure at trough from baseline to Day 84, the step-up trend test in the ITT LOCF Population was only significant for the placebo to nebivolol 20 mg contrast.

Due to the small number of patients in the various subgroups, no definitive conclusions from the data were apparent.

11.2 NEB-305 (Pivotal) ("A Double-Blind, Multi-Center, Randomized, Placebo-Controlled, Parallel Group Study of the Effects of Nebivolol on Safety and Efficacy in Patients with Mild to Moderate Hypertension")

Investigators

The 94 investigators are listed in Table 95 below. The 94 sites were located in the United States, Belgium, the United Kingdom, and the Netherlands. Individual sites randomized between 0 and 62 patients.

Table 95. Investigators (Study NEB-305)

Investigator	Site	# Pts	Investigator	Site	# Pts
		4			8
		18			3
		14			19
		6			1
		6			62
		0			9
		7			5
		5			5
		14			4
		0			26
		34			0
		10			0
		11			4
		0			1
		0		ed	15
		17			1
		1			7
		0			11
		1			4
		0			5
		19			6
		24			5
		7			0
	n	5			29
		0			1
		8			8
		3			21
		19			12
		3			1
		6			11

(continued)

Table 95. Investigators (Study NEB-305) (continued)

Investigator	Site	# Pts	Investigator	Site	# Pts
		1			6
		5			3
		4			2
		2			25
		11			8
		17			2
		10			25
		1			8
		6			1
		18			9
		20			0
		3			2
		4			3
		4			24
		2			36
		6			0
		11			6

Study Dates

September 17, 2001 – March 21, 2003

Study Design

This study description was based on the final protocol dated June 13, 2001 and amendments dated July 27, 2001[26] and March 13, 2002.[27]

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[26] **The first amendment made a variety of minor changes, including clarifying inclusion criteria. If patients were previously on antihypertensive therapy, Amendment 1 stated patients with a DBP > 80 and ≤ 109 mm Hg were eligible for screening. Amendment 1 also defined blood pressure warning levels, required unscheduled visits to be reported to the ——— and required serious adverse events to be reviewed by an independent monitor.**

[27] **The second amendment included a reference on the use of diuretics with nebivolol and altered exclusion criteria. Steroids and obese patients (BMI > 35 kg/m^2) were excluded from the study. Centrally acting alpha agonists were prohibited. Regarding restricted medication, continuous NSAID use was allowed up to 5 days, and the daily dose of acetylsalicylic acid could not exceed 162 mg. SSRIs were also allowed if the patient had been on a stable dose for three months. The site was instructed to call TeleTrial® prior to randomization. An additional screening visit (Visit 2a) was incorporated in the event patients were not over 90% compliant during the placebo run-in or needed extra time to satisfy the inclusion criteria. No waist circumferences were performed. Due to a typographical error, instead of the exclusion criteria being a BMI > 35 kg/m^2 (protocol), the CRF recorded it as ≥ 35 kg/m^2. Numerous statistical changes were made. Additions to the protocol-defined statistical plan included a summarization of baseline characteristics on all**

This was a Phase III, multi-center, multi-national, randomized, double-blind, parallel group, placebo-controlled study. The study design for Study NEB-305 was identical to that of Study NEB-302, except there was no pharmacokinetic sampling and patients were randomized to placebo or nebivolol 5, 10, or 20 mg orally qd for 84 days. The goal was to randomize 74 placebo and 726 nebivolol patients.

Baseline assessments and study drug dosing were identical to Study NEB-302. Investigators measured trough vital signs during all 7 clinic visits and peak vital signs during Visits 3 (Day 0), 5 (Day 28), and 7 (Day 84).

In Study NEB-305, the inclusion and exclusion criteria were the same as those in Study NEB-302, except that waist circumference was no longer an exclusion criteria in Study NEB-305. Additionally, the prohibited and restricted medications in Study NEB-305 were the same as those listed in Study NEB-302. The definitions of major protocol violations and protocol deviations were identical between Studies NEB-302 and NEB-305.

In patients with mild to moderate hypertension, the sponsor's objectives were to determine if nebivolol was superior to placebo for treatment of elevated blood pressure and to evaluate the safety and efficacy of nebivolol.

The primary endpoint was change of the average sitting diastolic blood pressure taken at trough (24 ± 2 hours post-previous morning's dose) at the end of treatment (Day 84) compared to baseline. Both Studies NEB-305 and NEB-302 shared the same primary endpoint.

The primary analysis was intention-to-treat (ITT) with the last observation carried forward (LOCF). A step-down trend test was the primary statistical method used for comparison of continuous variables in an ANCOVA model. For both sitting DBP and SBP at trough, a step-up trend test using a linear contrast in ANCOVA was performed as a secondary analysis. Overall treatment effect was assessed after adjustment for baseline differences and treatment-by-center interaction.

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[27] **(continued) randomized patients to compare treated and untreated patients, the addition of a worst case analysis on the primary efficacy parameter, an additional step-up trend test for the primary parameter and for one secondary parameter (change from baseline in sitting SBP at trough), additional adverse events analyses to compare all active treatment patients with placebo, and a summarization by ethnicity. In the final statistical analysis, the Chi-square test was used instead of Fisher's Exact test to evaluate demographic and baseline characteristics. Oxidative genotype and baseline blood pressure became new covariates. Instead of Koch's method, safety variables were analyzed using the CMH Test. A medical officer from _____ reviewed the SAEs, and there was no external safety monitoring board. The sponsor formally defined the PP population. Deviations from the final statistical plan included the discarding of the highest treatment group if step-down testing for categorical variables was statistically significant. For the ITT population, the sponsor allowed laboratory retesting results to be added at the end of the study. Only PP evaluations were carried forward for the PP LOCF. Trough was redefined from 22-36 hours post-dose (protocol) to 22-28 hours for the PP analyses.**

The secondary endpoints in Study NEB-305 were identical to those in Study NEB-302, except that there was no correlation between trough and peak plasma levels of nebivolol and change of average sitting diastolic blood pressure in Study NEB-305.

A medical reviewer [redacted] reviewed serious adverse events. There was no safety monitoring board.

Results (NEB-305)

The demographic and baseline characteristics of the subjects are presented in Table 96.

Table 96. Baseline Patient Characteristics by Treatment in Study NEB-305 (Population: Intent-to-Treat)

Parameter	Placebo n (%)	Nebivolol 5 mg n (%)	Nebivolol 10 mg n (%)	Nebivolol 20 mg n (%)	Total N (%)	p-value[a]
Age (years)						
N	75	244	244	244	807	0.287
Mean (SD)	51.2 (10.0)	53.9 (11.1)	53.8 (11.2)	53.4 (11.1)	53.4 (11.0)	
Median	50.0	54.0	53.0	53.0	53.0	
Range	27.0 to 73.0	23.0 to 79.0	22.0 to 82.0	28.0 to 80.0	22.0 to 82.0	
Age Group						
< 65	67 (89.3)	199 (81.6)	197 (80.7)	197 (80.7)	660 (81.8)	0.357
≥65	8 (10.7)	45 (18.4)	47 (19.3)	147 (18.2)		
Gender						
Male	39 (52.0)	131 (53.7)	131 (53.7)	131 (53.7)	432 (53.5)	0.994
Female	36 (48.0)	113 (46.3)	113 (46.3)	113 (46.3)	375 (46.5)	
Race						
Black	11 (14.7)	31 (12.7)	33 (13.5)	30 (12.3)	105 (13.0)	0.947
Non-Black	64 (85.3)	213 (87.3)	211 (86.5)	214 (87.7)	702 (87.0)	
Caucasian	60 (80.0)	190 (77.9)	191 (78.3)	192 (78.7)	633 (78.4)	
Asian	0 (0.0)	4 (1.6)	2 (0.8)	3 (1.2)	9 (1.1)	
Hispanic	4 (5.3)	19 (7.8)	17 (7.0)	19 (7.8)	59 (7.3)	
Other	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.1)	
Diabetes Status						
Yes	4 (5.3)	9 (3.7)	12 (4.9)	12 (4.9)	37 (4.6)	0.881
No	71 (94.7)	235 (96.3)	232 (95.1)	232 (95.1)	770 (95.4)	
Metabolism						
Poor	4 (5.3)	15 (6.1)	15 (6.1)	16 (6.6)	50 (6.2)	0.985
Extensive	71 (94.7)	229 (93.9)	229 (93.9)	228 (93.4)	757 (93.8)	
BMI (kg/m^2)						
< 30	48 (64.0)	152 (62.6)	145 (59.4)	137 (56.4)	482 (59.9)	0.473
≥ 30	27 (36.0)	91 (37.4)	99 (40.6)	106 (43.6)	323 (40.1)	
Missing[4]	0	1	0	1	2	

(a) From ANOVA with main effect treatment for continuous variables; From a Chi-Square Test for discrete variables
(b) Test of race is black vs. non-black
(c) BMI is the baseline weight in kilograms divided by the square of the baseline height in meters
(d) Missing not used in percentage calculation or testing
Cross Reference: Data Listings 1, 10.1.1-10.1.3, 10.4, and 14.3

(Reproduced from Sponsor, Table 1.1.1, pages 119 and 120)

Age, age group, diabetes status, weight, height, supine diastolic blood pressure, sitting diastolic blood pressure, and standing diastolic blood pressure , were statistically significantly different between Blacks and Non-Blacks in the ITT Nebivolol Population at baseline. Baseline patient characteristics by race are shown in Table 97 below.

Table 97. Baseline Patient Characteristics by Race (ITT Nebivolol Patients) in Study NEB-305

Parameter	Black	Non-Black	p-value[a]
Age (years)			
N	94	638	< 0.001
Mean	49.3 (10.3)	54.3 (11.1)	
Median	48.0	54.5	
Range	27.0 to 74.0	22.0 to 82.0	
Age group			
< 65	85 (90.4)	508 (79.6)	0.013
≥ 65	9 (9.6)	130 (20.4)	
Diabetes Status			
Yes	8 (8.5)	25 (3.9)	0.045
No	86 (91.5)	613 (96.1)	
Weight (kg)			
N	94	638	0.006
Mean (SD)	88.6 (16.9)	83.8 (15.4)	
Median	90.0	82.3	
Range	45.5 to 125.5	45.0 to 132.7	
Height			
N	94	636	0.044
Mean (SD)	172.2 (10.3)	169.9 (10.2)	
Median	170.0	170.0	
Range	152.0 to 198.0	137.0 to 201.0	
Supine Diastolic Blood Pressure			
N	94	638	0.018
Mean (SD)	99.3 (6.6)	97.7 (5.8)	
Median	99.0	97.0	
Range	80.0 to 119.0	73.0 to 119.0	
Sitting Diastolic Blood Pressure			
N	94	638	0.010
Mean (SD)	100.0 (4.4)	98.9 (3.9)	
Median	99.0	98.0	
Range	91.0 to 119.0	80.0 to 112.0	
Standing Diastolic Blood Pressure			
N	94	638	0.023
Mean (SD)	100.5 (5.2)	99.1 (5.7)	
Median	100.0	99.0	
Range	87.0 to 119.0	74.0 to 122.0	

(a) From ANOVA with main effect race for continuous variables from a Chi-Square Test for discrete variables
(b) BMI is the baseline weight in kilograms divided by the square of the baseline height in meters
Cross Reference: Data Listings 1, 10.1.1-10.1.3, 10.4, and 14.3

(Adapted from Sponsor, Tables 7.1 and 7.2, pages 567-569)

Common co-existing conditions in over 5% of patients included essential hypertension (99.9%), hypercholesterolemia (10.5%), hyperlipidemia (8.9%), hysterectomy (8.8%), seasonal allergies (5.7%), post-menopausal status (5.2%), and depression (5.1%).

The sponsor found that more nebivolol than placebo patients used concomitant medications during double-blind therapy. The most common concomitant medications used in ≥ 5% of patients included acetylsalicylic acid (13.8%), multivitamins (10.3%), paracetamol/acetaminophen (8.9%), atorvastatin (6.2%), and ibuprofen (5.0%).

Subject disposition is shown in Table 98 below.

Table 98. Patient Disposition (ITT Population) in Study NEB-305

Study Status	Placebo	Nebivolol 5 mg n (%)	Nebivolol 10 mg n (%)	Nebivolol 20 mg n (%)	Total N (%)
Screened	-	-	-	-	1288[a]
Enrolled	-	-	-	-	1138
Randomized	-	-	-	-	811
ITT	75	244	244	244	807
Completed	61 (81.3%)	218 (89.3%)	206 (84.4%)	217 (88.9%)	702 (87.0%)
Discontinued	14 (18.7%)	26 (10.7%)	38 (15.6%)	27 (11.1%)	105 (13.0%)
Adverse Event	4 (5.3%)	3 (1.2%)	9 (3.7%)	8 (3.3%)	24 (3.0)[b,c]
Treatment Failure	3 (4.0%)	3 (1.2%)	5 (2.0%)	3 (1.2%)	14 (1.7)
Lost to Follow-Up	0 (0.0%)	4 (1.6%)	8 (3.3%)	3 (1.2%)	15 (1.9)
Protocol Deviation	1 (1.3%)	0 (0.0)	3 (1.2%)	0 (0.0%)	4 (0.5)
Withdrew Consent	4 (5.3%)	8 (3.3%)	4 (1.6)	7 (2.9%)	23 (2.9)
Other	2 (2.7%)	8 (3.3%)	9 (3.7)	6 (2.5%)	25 (3.1)[c]

Data Source: Tables 1.8.1 and 1.8.2

[a] Two patients were counted twice in the total number of screened patients because they were screened twice. Patient 1642000965 and 1642001741 are the same patient who failed screening once (withdrew consent) and qualified the second time as 1642001741. Patient 2662000585 and 2662001167 are the same patient who failed screening the first time (did not meet inclusion/exclusion criteria) and qualified the second time as 2662001167.

[b] Two of these patients, 1662000813 and 2882000950 (nebivolol 10 and 20 mg), withdrew during double-blind treatment due to adverse events with onset during single-blind treatment.

[c] Patient 1662003432 (placebo) was listed as discontinuing due to Other (non-compliance) on the patient status page of the CRF; however, the patient was also listed as discontinuing due to an adverse event on the AE page of the CRF. To follow the most conservative approach, the patient is listed as discontinuing due to adverse event in this table, whereas, in the database and Table 1.8.1, the patient is listed as discontinued due to other (non-compliance)

(Reproduced from Sponsor, Table 10.1-01, page 57)

One investigator requested the blind be broken for Patient 7242000988 (nebivolol 5 mg) who developed a ruptured aortic aneurysm. The patient was withdrawn from the study. Patient 1902000153, recorded on the CRF as unblinded, was not unblinded per TeleTrial records but was discontinued due to a protocol deviation.

In the ITT Population, the sponsor's analysis of non-compliance (outside ± 10% of randomized dose) gave rates of 9.5% in the placebo group and a range from 5.5% to 7.8% in the nebivolol groups. The highest noncompliance rate was 7.8% in the nebivolol 10 mg group. The p-value, using a Chi-Square Test, was 0.555 for noncompliance in the placebo compared to nebivolol groups.

Primary Efficacy Endpoint (NEB-305)

For the primary efficacy endpoint, the sponsor's step-down trend testing found the linear contrasts for nebivolol 5, 10, and 20 mg in the ITT LOCF Population statistically significant. The LS mean change from baseline to end of study, along with the results of step-down and step-up trend testing, are listed in Table 99 below.

Table 99. LS Mean Change from Baseline to End of Study in Sitting Diastolic Blood Pressure at Trough and Trend Tests (ITT LOCF) (NEB-305)

Treatment	N	Baseline Mean	Treatment Mean	Mean Change from Baseline (SD)	LS Mean Change from Baseline (SE)	Step-down Trend Test p-value[a,b]	Step-up Trend Test p-value[a,c]
Placebo	75	98.7	91.4	-7.2 (8.2)	-4.6 (1.3)	-	< 0.001
Nebivolol							
5 mg	244	99.1	88.5	-10.6 (7.7)	-7.8 (1.0)	0.002	0.060
10 mg	244	98.9	87.7	-11.2 (8.1)	-8.5 (1.0)	< 0.001	0.360
20 mg	244	99.2	87.2	-12.0 (8.4)	-9.1 (1.0)	< 0.001	

Data Source: Table 2.1.1
[a] From an ANCOVA with factor treatment and covariates (baseline blood pressure, metabolism rate, diabetes status, gender, race, and age group)
[b] Step-down testing scheme began with treatments placebo through nebivolol 20 mg and proceeded to step down until the trend test contained only nebivolol 5 mg and placebo
[c] Step-up testing scheme began with treatments placebo through nebivolol 20 mg and proceeded to step up until the trend test contained only the 10 and 20 mg doses of nebivolol

(Reproduced from Sponsor, Table 11.4-02, page 65)

At day 84, The ITT OC and PP LOCF Population step-down trend results supported the ITT LOCF analysis. In the PP OC Population at day 84, however, only the nebivolol 20 mg contrast was statistically significant.

Step-up trend testing for sitting DBP at trough in the ITT LOCF Population was only significant for the placebo to nebivolol 20 mg contrast at the end of treatment. On Days 14 and 28, step-up trend testing was significant for all linear contrasts, but by Day 56, only the placebo and 5 mg contrasts were significant. Based on these results, the sponsor suggests differences between nebivolol doses decrease over time.

Differences from Placebo in LS Mean Change from Baseline in Sitting DBP at Trough (NEB-305)

In the ITT LOCF Population, the difference from placebo in LS mean change from baseline to end of study for the primary efficacy endpoint was statistically significant for nebivolol 5, 10, and 20 mg. The difference from placebo is shown in Table 100. The ITT OC and PP LOCF results supported the ITT LOCF analysis. For the PP OC Population, however, only the nebivolol 20 mg difference from placebo was significant at the end of the study.

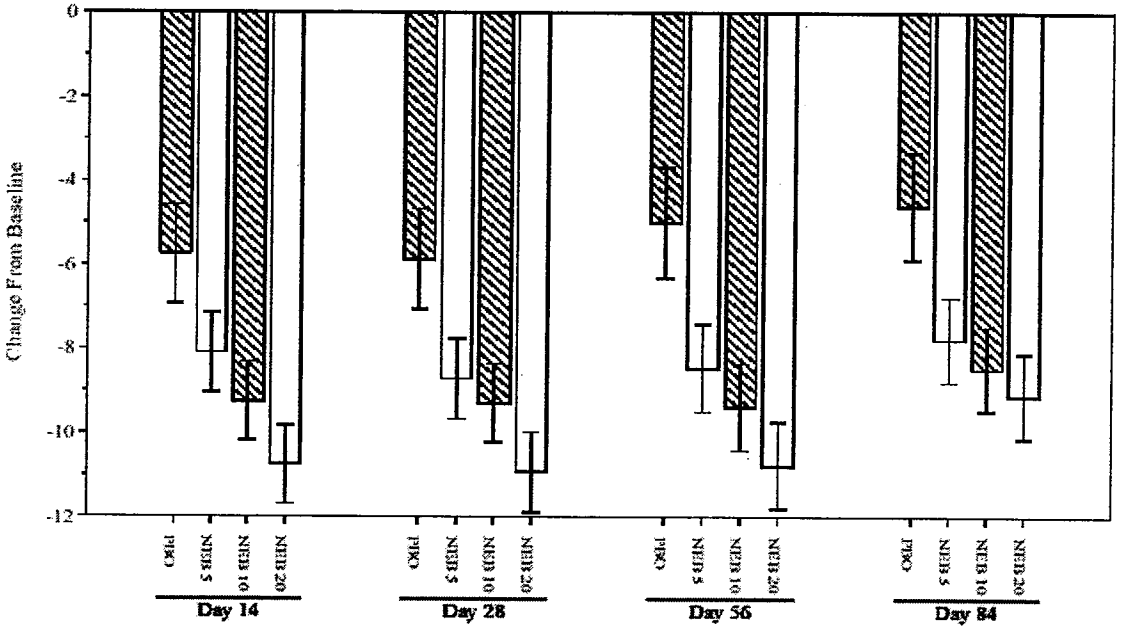
Table 100. Differences from Placebo in LS Mean Change from Baseline to End of Study in Sitting DBP (mm Hg) at Trough (ITT LOCF) (NEB-305)

Treatment Group	N	LS Mean Difference[a,b]	95% CIa,b	p-value[a,b]
Nebivolol				
5 mg	244	-3.2	(-5.2, -1.1)	0.002
10 mg	244	-3.9	(-5.9, -1.8)	< 0.001
20 mg	244	-4.5	(-6.6, -2.5)	< 0.001

Data Source: Table 2.1.1
[a] From an ANCOVA with factor treatment and covariates (baseline blood pressure, metabolism rate, diabetes status, gender, race, and age group)
[b] Pairwise comparison of treatment vs. placebo based on LS mean difference
(Reproduced from Sponsor, Table 11.4-03, page 66)

The sponsor graphically depicts the LS mean change in sitting DBP (trough) from baseline to end of study by visit for the ITT LOCF population in Figure 14 below.

Figure 18. Bar Graph of LS Mean Change from Baseline to End of Study in Sitting DBP (mm Hg) at Trough by Treatment +/- SE (ITT LOCF) (NEB-305)



Data Source: Figure 1.1.2
(Reproduced from Sponsor, Figure 11.4-02, page 68)

LS mean changes in sitting DBP at trough from baseline to end of study were comparable for both US and European sites.

Using the ITT Worst Case scenario, comparing mean change from baseline in sitting diastolic blood pressure at trough, nebivolol 5 mg, 10 mg, and 20 mg doses were significantly effective ($p = 0.005$ for nebivolol 5 mg, $p = 0.002$ for nebivolol 10 mg, and $p < 0.001$ for nebivolol 20 mg)

in step-down trend testing. The step-up trend test at the end of the study was significant only for the placebo to nebivolol 20 mg contrast ($p < 0.001$).

GCP Issues (NEB-305)

According to Bertek, Sites 117 and 263 were potential violators of GCP guidelines. The FDA previously cited the principal investigator at Site 117 for falsifying records in a different study. At Site 263, subjects returned 3 study medication bottles containing hydrochlorothiazide, which were not from the nebivolol study. After excluding these sites, Bertek reanalyzed the LS mean change in sitting DBP at trough from baseline to end of study in the ITT LOCF Population using step-up and step down trend testing. Nebivolol 5, 10, and 20 mg still significantly lowered diastolic blood pressure using step-down trend testing ($p < 0.003$). In step-up trend testing, only the placebo to nebivolol 20 mg contrast was significant ($p < 0.001$).

After excluding Sites 117 and 263, the differences from placebo in LS mean change from baseline to end of study in sitting diastolic blood pressure at trough in the ITT LOCF Population were still statistically significant ($p \leq .003$). The LS mean difference ranged from -3,1 mm Hg in the nebivolol 5 mg treatment group to -4.3 mm Hg in the nebivolol 10 mg treatment group.

Secondary Efficacy Endpoints (NEB-305)

Sitting Systolic Blood Pressure at Trough

For the ITT LOCF Population, using the step-down trend test for sitting SBP at trough from baseline to end of study, only nebivolol 20 mg was significant. At the other study visits for the ITT LOCF Population, all doses of nebivolol were statistically significant except for nebivolol 5 mg on Day 14. At Day 84, the ITT OC and PP LOCF analyses supported the ITT LOCF results in that only nebivolol 20 mg was statistically significant. For the PP OC Population, no doses of nebivolol were statistically significant at the end of study. The results of the ITT LOCF analysis are summarized in Table 101 below.

Table 101. Mean Change from Baseline to End of Study in Sitting Systolic Blood Pressure (mm Hg) at Trough and Trend Tests (ITT LOCF) (NEB-305)

Treatment	N	Baseline Mean	Treatment Mean	Mean Change from Baseline (SD)	LS Mean Change from Baseline (SE)[a]	Step-down Trend Test p-value[a,b]	Step-up Trend Test p-value[a,c]
Placebo	75	149.9	142.1	-7.9 (12.8)	-0.4 (2.2)	-	< 0.001
Nebivolol							
5 mg	244	151.8	139.7	-12.1 (14.1)	-4.2 (1.7)	0.035*	0.036
10 mg	244	150.5	139.8	-10.7 (14.8)	-3.5 (1.7)	0.086	0.008
20 mg	244	151.9	137.4	-14.6 (15.4)	-6.7 (1.7)	< 0.001	-

Data Source: Table 2.2.1

* p-value associated with lower dose not applicable in the context of step-down trend testing due to the non-significant result at the higher dose.

[a] From an ANCOVA with factor treatment and covariates (baseline blood pressure, metabolism rate, diabetes status, gender, race, and age group).

[b] Step-down testing scheme began with treatments placebo through nebivolol 20 mg and proceeded to step down until the trend test contained only nebivolol 5 mg and placebo.

[c] Step-up testing scheme began with treatments placebo through nebivolol 20 mg and proceeded to step up

until the trend test contained only the 10 and 20 mg doses of nebivolol.
(Reproduced from Sponsor, Table 11.4-07, page 74)

Step-up trend testing in the ITT LOCF Population was statistically significant for all nebivolol doses (5, 10, and 20 mg).

For sitting SBP at trough to end of study in the ITT LOCF Population, only the pairwise difference from placebo to nebivolol 20 mg was statistically significant ($p < 0.001$).

Summary of Primary and Secondary Endpoints (NEB-305)
At trough and peak, step-down trend testing in the ITT LOCF Population for change in sitting, standing, or supine DBP from baseline to end of study was significant for nebivolol 5, 10, and 20 mg.

For sitting, standing, or supine systolic blood pressure at trough, step-down trend testing in the ITT LOCF Population was only significant for nebivolol 20 mg. At peak, step-down trend testing for change in sitting, standing, or supine systolic blood pressure was significant for all nebivolol doses with the exception of nebivolol 5 mg for sitting systolic blood pressure.

Table 102 below and Table 103 summarize the step-down trend testing results for LS mean change in DBP and SBP at trough and peak from baseline to end of study.

Table 102. Summary of Results of the Step-Down Trend Test and LS Mean Change in DBP and SBP (mm Hg) from Baseline to End of Study (Day 84) at Trough (ITT LOCF) (NEB-305)

	Sitting			Standing			Supine		
	p-value[a,b]	LS Mean[c]	LS Mean Diff	p-value[a,b]	LS Mean[c]	LS Mean Diff	p-value[a,b]	LS Mean[c]	LS Mean Diff
Placebo									
DBP	---	-4.6	---	---	-3.7	---	---	-3.4	---
SBP	---	-0.4	---	---	-0.9	---	---	1.0	---
Nebivolol 5 mg									
DBP	0.002	-7.8	-3.2	0.002	-6.9	-3.2	<0.001	-7.8	-4.4
SBP	0.035*	-4.2	-3.8	0.016*	-5.3	-4.4	0.012*	-3.6	-4.6
Nebivolol 10 mg									
DBP	<0.001	-8.5	-3.9	<0.001	-7.2	-3.5	<0.001	-7.7	-4.3
SBP	0.086	-3.5	-3.1	0.107	-3.8	-3.0	0.082	-2.2	-3.2
Nebivolol 20 mg<									
DBP	<0.001	-9.1	-4.5	<0.001	-8.1	-4.4	<0.001	-8.4	-5.0
SBP	<0.001	-6.7	-6.3	0.002	-7.2	-6.4	<0.001	-5.9	-7.0

Data Source: Tables 2.1.1, 2.2.1, 2.5.1, 2.6.1, 2.9.1, and 2.10.1
* **p-value associated with lower dose not applicable in the context of step-down trend testing due to the nonsignificant result at the higher dose.**
[a] **p-vale from step-down trend test; step-down testing begins with placebo to nebivolol 20 mg and proceeds to step down until the test contains only placebo and nebivolol 5 mg**
[b] **From an ANCOVA with factor treatment and covariates baseline blood pressure, EM or PM classification, diabetes status, gender, race, and age group**
[c] **LS mean change in DBP or SBP from baseline to end of study**

(Reproduced from Sponsor, Table 11.4-13, page 88)

Table 103. Summary of Results of the Step-Down Trend Test and LS Mean Change in DBP and SBP (mm Hg) from Baseline to End of Study (Day 84) at Peak (ITT LOCF) (NEB-305)

	Sitting			Standing			Supine		
	p-value[a,b]	LS Mean[c]	LS Mean Diff	p-value[a,b]	LS Mean[c]	LS Mean Diff	p-value[a,b]	LS Mean[c]	LS Mean Diff
Placebo									
DBP	---	-7.0	---	---	-6.3	---	---	-6.1	---
SBP	---	-4.7	---	---	-3.1	---	---	-2.1	---
Nebivolol 5 mg									
DBP	<0.001	-10.5	-3.5	<0.001	-10.1	-3.8	<0.001	-10.8	-4.7
SBP	0.069	-7.7	-3.1	0.005	-8.0	-5.0	0.002	-7.5	-5.4
Nebivolol 10 mg									
DBP	<0.001	-11.6	-4.6	<0.001	-11.7	-5.4	<0.001	-11.0	-4.9
SBP	0.004	-9.5	-4.9	<0.001	-9.3	-6.2	<0.001	-7.8	-5.7
Nebivolol 20 mg≤									
DBP	<0.001	-12.2	-5.2	<0.001	-11.8	-5.5	<0.001	-11.4	-5.3
SBP	<0.001	-10.7	-6.0	<0.001	-10.7	-7.6	<0.001	-9.3	-7.2

Data Source: Tables 2.3.1, 2.4.1, 2.7.1, 2.8.1, 2.11.1, and 2.12.1
[a] p-vale from step-down trend test; step-down testing begins with placebo to nebivolol 20 mg and proceeds to step down until the test contains only placebo and nebivolol 5 mg
[b] From an ANCOVA with factor treatment and covariates baseline blood pressure, EM or PM classification, diabetes status, gender, race, and age group
[c] LS mean change in DBP or SBP from baseline to end of study

(Reproduced from Sponsor, Table 11.4-14, page 89)

Subgroup Analyses (NEB-305)

Change in Sitting DBP at Trough by Subgroup

The sponsor performed subgroup analyses (race, age, diabetes status, metabolism of nebivolol, and gender) on the primary endpoint , change in sitting diastolic blood pressure at trough from baseline to end of study in the ITT LOCF Population. For evenly distributed subgroups of gender and BMI, there were dose-dependent decreases in sitting DBP at trough from baseline to end of study. For race, age, and EM/PM classification subgroups, however, there was an unequal distribution of these patients and an inadequate sample size. Although there were consistent decreases in sitting DBP at trough over placebo, no definitive conclusions could be made.

The diabetic subgroup also had small numbers of patients, so no definitive conclusions could be made. There were only 4 diabetics in the placebo group, which had a large LS mean reduction in diastolic blood pressure of 11.8 mm Hg. When the LS mean reductions from diabetics taking nebivolol were compared to placebo, there was actually an increase of from 1.9 mm Hg to 3.4 mm Hg in diastolic blood pressure at trough, despite each nebivolol group experiencing decreases in the LS mean from -7.7 to -9.9 mm Hg.

In Study NEB-305, only 8 placebo patients were ≥ 65 years of age. Additionally, in each nebivolol dosing group, there were only 45 to 47 patients ≥ 65 years of age. When the LS mean results from the nebivolol group were compared to placebo, nebivolol patients ≥ 65 years of age had smaller LS mean differences than nebivolol patients < 65 years of age.

The summary of change in trough sitting DBP from baseline to end of study by subgroup is shown in Table 104 and Table 105.

Table 104. Summary of Change in Sitting DBP (mm Hg) at Trough from Baseline to End of Study by Subgroup (Race, Age, and Gender; ITT LOCF) (NEB-305)

	Race						Age						Gender					
	Black			Non-Black			<65			≥65			Male			Female		
	N	LS Mean[a] (SE)	LS Mean Diff[b,c]	N	LS Mean[a] (SE)	LS Mean Diff[b,c]	N	LS Mean[a] (SE)	LS Mean Diff[b,c]	N	LS Mean[a] (SE)	LS Mean Diff[b,c]	N	LS Mean[a] (SE)	LS Mean Diff[b,c]	N	LS Mean[a] (SE)	LS Mean Diff[b,c]
Placebo	11	-5.3 (3.6)	—	64	-5.9 (1.4)	—	67	-3.9 (1.4)	—	8	-9.6 (3.4)	-	39	-5.7 (1.8)	—	36	-3.9 (1.8)	—
Nebivolol																		
5mg	31	-10.7 (3.2)	-5.3	212	-8.9 (1.1)	-3.0	198	-7.6 (1.2)	-3.7	45	-9.9 (2.1)	-0.2	130	-8.5 (1.5)	-2.9	113	-7.5 (1.4)	-3.6
10mg	33	-8.2 (3.0)	-2.9	211	-10.0 (1.1)	-4.2	197	-8.1 (1.1)	-4.2	47	-11.1 (2.1)	-1.4	131	-9.5 (1.4)	-3.8	113	-7.6 (1.4)	-3.7
20mg	30	-8.7 (2.9)	-3.4	213	-10.8 (1.0)	-4.9	196	-8.8 (1.1)	-5.0	47	-11.8 (2.1)	-2.2	131	-9.4 (1.4)	-3.7	112	-9.3 (1.5)	-5.4

Data Source: Table 2.15
[a] LS mean change in DBP from baseline to end of study
[b] From an ANCOVA with factor treatment and covariates baseline blood pressure, EM or PM classification, diabetes status, gender, race, BMI group and age group with covariates from the analysis removed from the model
[c] Pairwise comparison of treatment vs. placebo based on LS mean difference

(Reproduced from Sponsor, Table 11.4-16, page 94)

Table 105. Summary of Change in Sitting DBP (mm Hg) at Trough from Baseline to End of Study by Subgroup (BMI, Diabetes Status, and EM/PM Classification; ITT LOCF) (NEB-305)

	BMI						Diabetes Status						EM/PM Classification					
	<30kg/m^2			≥30kg/m^2			Diabetes			No Diabetes			PM			EM		
	N	LS Mean[a] (SE)	LS Mean Diff[b,c]	N	LS Mean[a] (SE)	LS Mean Diff[b,c]	N	LS Mean[a] (SE)	LS Mean Diff[b,c]	N	LS Mean[a] (SE)	LS Mean Diff[b,c]	N	LS Mean[a] (SE)	LS Mean Diff[b,c]	N	LS Mean[a] (SE)	LS Mean Diff[b,c]
Placebo	48	-4.4 (1.9)	—	27	-5.1 (1.8)	—	4	-11.8 (4.9)	—	71	-4.9 (1.2)		4	-5.7 (5.6)	—	71	-5.2 (1.2)	—
Nebivolol																		
5mg	152	-7.6 (1.5)	-3.2	91	-9.0 (1.5)	-3.9	9	-9.9 (3.4)	1.9	234	-8.5 (0.8)	-3.7	15	-9.8 (3.6)	-4.1	228	-8.4 (0.9)	-3.2
10mg	145	-8.3 (1.6)	-3.9	99	-9.4 (1.4)	-4.3	12	-7.7 (3.0)	4.1	232	-9.3 (0.8)	-4.4	15	-9.3 (3.2)	-3.6	229	-9.2 (0.8)	-4.0
20mg	137	-9.5 (1.6)	-5.1	106	-9.4 (1.4)	-4.4	12	-8.4 (3.9)	3.4	231	-9.9 (0.8)	-5.1	16	-10.8 (3.0)	-5.1	227	-9.7 (0.9)	-4.5

Data Source: Table 2.15
[a] LS mean change in DBP from baseline to end of study
[b] From an ANCOVA with factor treatment and covariates baseline blood pressure, EM or PM classification, diabetes status, gender, race, BMI group and age group with covariates from the analysis removed from the model
[c] Pairwise comparison of treatment vs. placebo based on LS mean difference

(Reproduced from Sponsor, Table 11.4-17, page 95)

Analyses by Race (NEB-305)

For the ITT LOCF Population, there was no significant interaction by race for change in sitting DBP at trough from baseline to end of treatment ($p > 0.1$).

For all subgroups by race, the mean change from baseline in sitting DBP at trough was more pronounced in Non-Blacks than in Blacks taking nebivolol, as seen in Table 106. In some of the subgroups, however, the overall number of Blacks is small, so no definitive conclusions can be made.

Table 106. Mean Change from Baseline in Trough Sitting Diastolic Blood Pressure (mm Hg) at Day 84 (Population: Intent-to-Treat Last Observation Carried Forward Nebivolol Patients[a]) (NEB-305)

Parameter	Blacks				Non-Blacks			
	n (%)	Baseline Mean	Day 84 Mean	Change Mean	n (%)	Baseline Mean	Day 84 Mean	Change Mean
Age Group								
< 65	85 (90.4)	100.2	92.5	-7.7	508 (79.6)	99.1	87.3	-11.8
≥ 65	9 (9.6)	98.1	85.3	-12.8	130 (20.4)	97.9	86.6	-11.3
Gender								
Male	46 (48.9)	101.0	93.7	-7.3	347 (54.4)	99.1	88.6	-10.5
Female	48 (51.1)	99.1	90.1	-9.0	291 (45.6)	98.6	85.5	-13.1
Diabetes Status								
Yes	8 (8.5)	98.0	91.3	-6.8	25 (3.9)	98.7	90.2	-8.6
No	86 (91.5)	100.2	91.9	-8.3	613 (96.1)	98.9	87.1	-11.8
EM or PM Classification								
Poor	3 (3.2)	100.3	90.7	-9.7	43 (6.7)	97.3	87.3	-10.1
Extensive	91 (96.8)	100.0	91.9	-8.2	595 (93.3)	99.0	87.2	-11.8
BMI[b] (kg/m²)								
< 30	53 (56.4)	100.3	92.1	-8.2	381 (59.9)	98.7	86.5	-12.2
≥ 30	41 (43.6)	99.7	91.5	-8.2	255 (40.1)	99.1	88.2	-10.9

(a) Only Nebivolol treatments are pooled for this analysis
(b) BMI is the baseline weight in kilograms divided by the square of the baseline height in meters
Cross Reference: Data Listings 1, 10.1.1, 10.2.1, 10.4, and 14.3

(Reproduced from Sponsor, Table 7.5, page 572)

Response Rates (NEB-305)

The definition of a responder for Study NEB-305 was the same as for Study NEB-302. In the ITT LOCF Population, there were significantly more responders compared to placebo in all nebivolol groups, as shown in Table 107 below.

Table 107. Responder Rates[a] by Treatment (Evaluation of Possible Predictors of Responders) (ITT LOCF) (NEB-305)

Treatment	Total N	Responder n (%)[b]	p-value[c]
Placebo	75	37 (49.3)	
Nebivolol 5 mg	244	161 (66.0)	0.009
Nebivolol 10 mg	244	163 (66.8)	0.005
Nebivolol 20 mg	244	168 (68.9)	0.002

[a] A subject is a responder if their average trough sitting diastolic blood pressure < 90 mm Hg at end of study or has decreased by ≥ 10 mm Hg from baseline
[b] Percentage is the percentage of responders within that category
[c] Based on Wald Chi-Square Test for trend from logistic regression with factor treatment and covariates baseline blood pressure, EM or PM classification, diabetes status, gender, race, and age group; Step-down testing scheme begins with treatments placebo through Nebivolol 20 mg and proceeds to step-down until the trend test contains only placebo and Nebivolol 5 mg
NS: P-values should not be used in the context of step-down trend testing (see analysis for explanation)
Cross Reference: Data Listings 1, 10.1.1, 10.2.1, 10.4, and 14.3

(Reproduced from Sponsor, Table 2.13.2, page 528)

The response rate increased over the duration of the study, although the rate seemed to plateau by Day 56, as shown in Table 108.

Table 108. Responder[a] Rates by Treatment and Visit (ITT LOCF) (NEB-305)

Visit	Placebo n (%)b	Nebivolol 5 mg n (%)[b]	Nebivolol 10 mg n (%)[b]	Nebivolol 20 mg n (%)[b]	Total n(%)[b]
Day 14	34 (45.3)	152 (62.3)	165 (67.6)	180 (73.8)	531 (65.8)
Day 28	41 (54.7)	160 (65.6)	172 (70.5)	183 (75.0)	556 (68.9)
Day 56	39 (52.0)	156 (63.9)	165 (67.6)	178 (73.0)	538 (66.7)
Day 84	37 (49.3)	161 (66.0)	163 (66.8)	168 (68.9)	529 (65.6)

[a] **A subject is a responder if their average trough sitting diastolic blood pressure < 90 mm Hg at endpoint of interest or has decreased by ≥ 10 mm Hg from baseline**
[b] **Percentage is the percentage of responders within that category**
Cross Reference: Data Listings 10.1.1, 10.2.1, and 10.4

(Reproduced from Sponsor, Table 2.13.5, page 532)

Response Rate by Subgroup (NEB-305)

The small number of patients in some subgroups and the placebo population make these results difficult to interpret. Overall, however, women and non-Blacks had significantly higher response rates than men and Blacks, respectively, as seen in Table 109.

Table 109. Responder[a] Rates by Treatment and Baseline Characteristic at Day 84 (End of Study) (Population: Intent-to-Treat Last Observation Carried Forward) (NEB-305)

Characteristic Subgroup	Placebo n (%)[b]	Nebivolol 5 mg n (%)[b]	Nebivolol 10 mg n (%)[b]	Nebivolol 20 mg n (%)[b]	Total n (%)[b]	Subgroup p-value[c]
Age						
< 65	31 (46.3)	130 (65.3)	129 (65.5)	138 (68.0)	424 (64.2)	0.566
≥ 65	6 (75.0)	31 (68.9)	34 (72.3)	34 (72.5)	105 (71.4)	
Gender						
Male	18 (46.2)	78 (59.5)	84 (64.1)	80 (61.1)	260 (60.2)	<0.001
Female	19 (52.8)	83 (73.5)	79 (69.9)	88 (77.9)	269 (71.7)	
Race						
Black	5 (45.5)	18 (58.1)	13 (39.4)	12 (40.0)	48 (45.7)	<0.001
Non-Black	32 (50.0)	143 (67.1)	150 (71.1)	156 (72.9)	481 (68.5)	
Diabetes Status						
Yes	3 (75.0)	7 (77.8)	5 (41.7)	5 (41.7)	20 (54.1)	0.233
No	34 (47.9)	154 (65.5)	158 (68.1)	163 (70.3)	509 (66.1)	
EM or PM Classification						
Poor	2 (50.0)	12 (80.0)	11 (73.3)	10 (62.5)	35 (70.0)	0.922
Extensive	35 (49.3)	149 (65.1)	152 (66.4)	158 (69.3)	494 (65.3)	

(a) A subject is a responder if their average trough sitting diastolic blood pressure < 90 mmHg at end of study or has decreased by ≥ 10 mmHg from baseline
(b) Percentage is the percentage of responders within that category
(c) Test of difference between subgroups based on Wald Chi-Square Test from logistic regression with factor treatment and covariates baseline blood pressure, EM or PM classification, diabetes status, gender, race, and age group
Cross Reference: Data Listings 1, 10.1.1, 10.2.1, 10.4, and 14.3

(Reproduced from Sponsor, Table 2.13.9, page 536)

Although the full logistic model suggests there is a "treatment by diabetes interaction" ($p = 0.088$), the number of diabetic patients enrolled in this study is small and no definitive conclusions can be drawn.

Trough to Peak Ratios

The placebo subtracted trough-to-peak ratios for change in sitting DBP from baseline to end of study are shown in Table 110.

Table 110. Placebo Subtracted Trough to Peak Ratio for Change from Baseline in Sitting Diastolic Blood Pressure at Day 84 (Population: Intent-to-Treat Last Observation Carried Forward) (Study NEB-305)

Treatment	N	Trough Mean	Peak Mean	Active - Placebo		
				Trough Mean	Peak Mean	Ratio
Placebo	75	-7.2	-10.1			
Nebivolol 5 mg	244	-10.6	-13.7	-3.4	-3.6	0.9
Nebivolol 10 mg	344	-11.2	-14.8	-4.0	-4.7	0.8
Nebivolol 20 mg	244	-12.0	-15.4	-4.7	-5.3	0.9
Cross Reference: Data Listings 10.1.1, 10.2.1, 10.3.1, and 10.4						

(Reproduced from Sponsor, Table 2.14, page 537)

Overall, 702/807 patients completed Study NEB-305. Fifteen patients (1.9%) were lost to follow-up. There were no deaths. According to the sponsor's analysis, major protocol violations and protocol deviations occurred in 33/75 (44.0%) placebo and 223/732 (30.4%) nebivolol patients. The sponsor indicated the most common major protocol violations were clinic visits (14.1%), trough blood pressure measurements (10.4%), and peak blood pressure measurements (8.4%) being outside acceptable time windows.

According to the sponsor, fourteen patients received the wrong medication bottles because study sites did not follow TeleTrial® results. Of these 14 patients, 1 patient failed screening and never took study drug medication, 8 patients received incorrectly labeled bottles of study medication, and 5 patients received the wrong study medication or dose.

Of the 8 patients who received incorrectly labeled bottles of study medication, 4 patients did not complete the study because the investigational site was closed for GCP violations, 1 patient experienced an adverse event and withdrew from the study, and 3 patients completed the study.

The following patients received the wrong study medication or dose.

Patient	Assigned to	Received	Comments
1542001046	Nebivolol 10 mg	Placebo	Received only 1 incorrect bottle of study medication but completed the study
1542003083	Nebivolol 10 mg	Nebivolol 20 mg	Received only 1 incorrect bottle of study medication but completed the study
727001439	Nebivolol 10 mg	Nebivolol 20 mg	Received only 1 incorrect bottle of study medication but completed the study
1632000168	Nebivolol 20 mg	Nebivolol 10 mg	Received only 1 incorrect bottle of study medication but completed the study
7252000136	Nebivolol 10 mg	Nebivolol 20 mg during placebo run-in and placebo at Visit 3 (Day 0)	Patient withdrawn due to protocol violation

Lastly, patient 1642003390 apparently received nebivolol 5 mg during the placebo run-in, as opposed to placebo. At Visit 4, this patient correctly received nebivolol 5 mg and completed the study.

Summary (NEB-305)

In the ITT LOCF Population, Nebivolol 2.5, 5, and 10 mg had statistically significant effects on the primary endpoint, change in sitting diastolic blood pressure from baseline until end of study. The ITT OC and PP LOCF results were similar to the ITT LOCF results at Day 84. In the PP OC Population at Day 84, however, only the nebivolol 20 mg contrast was statistically significant. In the step-up trend test for the ITT LOCF Population regarding the primary endpoint, only the placebo to nebivolol 20 mg contrast was statistically significant.

For secondary diastolic endpoints at trough and peak in the ITT LOCF population, nebivolol 2.5, 5, and 10 mg were statistically significant for the ITT LOCF Population while sitting, standing, or supine.

For secondary systolic endpoints at trough, only nebivolol 20 mg was statistically significant in step-down trend testing while sitting, standing, or supine.

For secondary systolic endpoints at peak, all nebivolol doses were significant with the exception of nebivolol 5 mg for sitting systolic blood pressure.

The trough to peak ratio was approximately 0.8 to 0.9 in the ITT LOCF population.

For the primary endpoint in the ITT LOCF Population, women and Non-Blacks had significantly higher response rates than men and Blacks, respectively.

Due to the small number of patients in some of the subgroups, no definitive conclusions from the data can be made.

11.3 NEB-202 (Pivotal) ("A Double-Blind, Multicenter, Randomized, Placebo-Controlled, Parallel Group Dosing Study of the Effects of Nebivolol on Blood Pressure in Black Patients with Mild to Moderate Hypertension")

Investigators

The 53 investigators are listed in Table 111 below. All 38 sites were in the US. Individual sites (n = 38) randomized between 0 and 30 patients.

Table 111. Investigators (Study NEB-202)

Investigator	Site	# Pts	Investigator	Site	#Pts
		0			6
		4			4
		7			0
		2			11
		0			10
		0			3
		13			11
		0			5
		0			0
		1			1
		2			0
		3			0
		1			3
		21			14
		8			10
		0			0
		4			9
		13			7
		1			4
		0			7
		5			20
		27	aced		2
		9			3
		0			2
		30			0
		4			4
		0			

Study Dates

November 1, 2001 – August 5, 2003

Study Design

This study description was based upon the protocol dated June 13, 2001 and amendments dated July 27, 2001,[28] March 13, 2002,[29] May 30, 2002,[30] and February 4, 2003.[31]

[28]**The first amendment made a variety of minor changes, including the clarification of inclusion/exclusion criteria and the definition of SBP warning levels. The sponsor also stated the Declaration of Helsinki would**

This was a Phase III double-blind, multi-center, randomized, placebo-controlled, parallel group dosing study. As in Study NEB-302 and NEB-305, Study NEB-202 had two phases. Phase I consisted of screening, followed by washout/single-blind placebo run-in (28-42 days). A minimum of 28 days was required for the run-in phase. If the patient had not been treated with antihypertensive therapy for over 30 days prior to enrollment, the run-in phase could be reduced to a minimum of 14 days. If patients previously on antihypertensive medication did not satisfy inclusion criteria after 28 days, they were allowed an additional 14 days of single-blind placebo run-in. After successful completion of Phase I, patients entered the double-blind Phase II and were randomized to placebo or nebivolol 2.5 mg, 5 mg, 10 mg, 20 mg, or 40 mg orally qd for 84 days. Unlike Study NEB-302, there was no dose-titration in any of the treatment arms. If patients were not currently on a hypertensive medication, the sponsor required 6 study visits. If patients were on a hypertensive medication, the sponsor required 7 study visits. After randomization, patients were followed biweekly for the first month and then monthly thereafter. The goal was to enroll 50 placebo and 250 nebivolol patients.

Baseline assessments included history, physical exam, 12-lead ECG, beta-HCG urine pregnancy test (for women), routine laboratory evaluation, and genomics testing for cytochrome P450-2D6 analysis. Investigators did not perform pharmacokinetic sampling in Study NEB-202.

Study medication was to be taken between 7 AM and 10 AM each day with or without breakfast. The investigator measured trough vital signs during all 7 clinic visits and peak vital signs during Visit 3 (Day 0), Visit 5 (Day 28), and Visit 7 (Day 84).

In Study NEB-202, the inclusion criteria were identical to those criteria described in Studies NEB-302 and NEB-305, with the exception of Study NEB-202 requiring patients to be Black.

In Study NEB-202, the exclusion criteria were identical to Studies NEB-302 and NEB-305, with one exception. The exclusion criterion for BMI in Study NEB-202 was > 40 kg/m^2, instead of $\geq$ 35 kg/m^2.

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be followed, with no specification of version date so the principles would be recognized by all regulatory agencies.

[29]**The second amendment prohibited the use of centrally acting alpha agonists, allowed the use of acetaminophen, and defined restricted medications. Additionally, the order of procedures was changed so TeleTrial® was contacted prior to laboratory/genomic sampling, and the sponsor clarified reasons for Visit 2a. Patients with indeterminate genomics testing would not be randomized or allowed to continue in the study.**

[30]**The third amendment changed exclusion criteria to a BMI > 40 kg/m^2, allowed restricted NSAID use, and restricted the use of SSRIs.**

[31]**The fourth amendment increased the total number of randomized patients from approximately 180 to approximately 300 and increased the number of patients per treatment group from 30 to approximately 50. The fourth amendment also stated a placebo run-in period of at least 14 days was required for those patients not previously on antihypertensive medications for over 30 days. Patients not previously on antihypertensive medications required at least 6 clinic visits. The amendment clarified that at Visits 3 and 7 (or the end of treatment), three 12-lead ECGs would be recorded 2 to 5 minutes apart prior to the administration of double-blind study drug and then again at approximately 2 hours post study drug administration. The fourth amendment made several other minor changes.**

The prohibited and restricted medications in Study NEB-202 were identical to those described in Studies NEB-302 and NEB-305.

In Black patients with mild to moderate hypertension, the sponsor's objectives were to determine if nebivolol was superior to placebo for the treatment of elevated blood pressure and to determine the dose-response relationship of nebivolol on blood pressure.

The primary endpoint was change of the average sitting diastolic blood pressure taken at trough (24 ± 2 hours post previous morning's dose) at the end of treatment compared to baseline. The primary endpoint was the same for Studies NEB-302, NEB-305, and NEB-202.

The primary analysis was intention-to-treat (ITT) with the last observation carried forward (LOCF). The secondary population for determination of efficacy was the Per-Protocol (PP) Population. The primary statistical method of treatment comparison for continuous variables was the step-down dose response trend test. For sitting DBP and SBP at trough, the sponsor performed a secondary dose-response step-up trend test with and without the 40 mg dose. The sponsor used two-sided statistical tests with a p value of 0.05. For the primary endpoint, covariate interaction in the ITT LOCF Population was evaluated at $p < 0.1$. Overall treatment effect was assessed after adjustment for baseline differences and treatment-by-center interaction. After analyses with placebo-subtracted results, subsequent analyses were performed comparing LS mean change in the nebivolol treatment groups to placebo.

The secondary endpoints were identical to those described in Study NEB-302, except no plasma nebivolol levels were evaluated in Study NEB-202.

Investigators reported serious adverse events to ———within 24 hours. There was no safety monitoring board for Study NEB-202.

Results (NEB-202)

The demographic and baseline characteristics are presented in Table 112. There were no statistically significant differences between subgroups in the baseline characteristics.

Table 112. Baseline Patient Characteristics by Treatment (ITT) (NEB-202)

Parameter	Placebo n(%)	Nebivolol 2.5 mg n (%)	Nebivolol 5 mg n (%)	Nebivolol 10 mg n(%)	Nebivolol 20 mg n (%)	Nebivolol 40 mg n (%)	Total N (%)	p-value[a]
Age								
N	49	49	50	51	50	51	300	0.800
Mean (SD)	49.7 (9.1)	49.9 (9.6)	51.6 (10.5)	50.5 (10.5)	51.3 (10.8)	52.3 (12.0)	50.9 (10.4)	
Median	49.0	49.0	51.0	49.0	51.5	51.0	50.0	
Range	34.0 to 70.0	33.0 to 75.0	26.0 to 77.0	29.0 to 79.0	28.0 to 74.0	28.0 to 79.0	26.0 to 79.0	
Age Group								
< 65	44 (89.8)	45 (91.8)	44 (88.0)	45 (88.2)	45 (90.0)	42 (82.4)	265 (88.3)	0.762
≥ 65	5 (10.2)	4 (8.2)	6 (12.0)	6 (11.8)	5 (10.0)	9 (17.6)	35 (11.7)	
Gender								
Male	23 (46.9)	26 (53.1)	22 (44.0)	22 (43.1)	21 (42.0)	22 (43.1)	136 (45.3)	0.890
Female	26 (53.1)	23 (46.9)	28 (56.0)	29 (56.9)	29 (58.0)	29 (56.9)	164 (54.7)	
Diabetes Status								
Yes	6 (12.2)	7 (14.3)	8 (16.0)	6 (11.8)	7 (14.0)	9 (17.6)	43 (14.3)	0.961
No	43 (87.8)	42 (85.7)	42 (84.0)	45 (88.2)	43 (86.0)	42 (82.4)	257 (85.7)	
Metabolism								
Poor	0 (0.0)	1 (2.0)	1 (2.0)	2 (3.9)	1 (2.0)	2 (3.9)	7 (2.3)	0.796
Extensive	49 (100.0)	48 (98.0)	49 (98.0)	49 (96.1)	49 (98.0)	49 (96.1)	293 (97.7)	
BMI (kg/m^2)								
< 30	21 (42.9)	26 (53.1)	26 (52.0)	26 (51.0)	25 (50.0)	20 (39.2)	144 (48.0)	0.672
≥ 30	28 (57.1)	23 (46.9)	24 (48.0)	25 (49.0)	25 (50.0)	31 (60.8)	156 (52.0)	

[a] From ANOVA with main effect treatment for continuous variables; From a Chi-Square Test for discrete variables
[c] BMI is the baseline weight in kilograms divided by the square of the baseline height in meters
Cross Reference: Data Listings 1 and 14.3

(Reproduced from Sponsor, Table 1.1.1, pages 132 and 133)

In regard to baseline vital signs for the ITT Population, however, there was a significant difference in sitting ($p = 0.027$) and standing DBP ($p = 0.040$) for the placebo and nebivolol 2.5, 5, 10, 20, and 40 mg treatment groups.

Table 113. Baseline Vital Signs, Weight, Height, and BMI by Treatment (ITT) (NEB-202)

Parameter	Placebo	Nebivolol 2.5 mg	Nebivolol 5 mg	Nebivolol 10 mg	Nebivolol 20 mg	Nebivolol 40 mg	Total	p-value[a]
Sitting Diastolic Blood Pressure (mm Hg)								
N	49	49	50	51	50	51	300	0.027
Mean (SD)	100.8 (4.0)	99.5 (4.3)	100.5 (4.4)	100.3 (4.6)	101.5 (4.7)	98.7 (3.9)	100.2 (4.4)	
Median	100.0	99.0	100.0	100.0	101.0	(99.0)	100.0	
Range	95.0 to 111.0	83.0 to 107.0	91.0 to 109.0	86.0 to 111.0	90.0 to 115.0	89.0 to 107.0	83.0 to 115.0	
Standing Diastolic Blood Pressure (mm Hg)								
N	49	49	50	51	50	51	300	0.040
Mean (SD)	101.1 (5.4)	99.2 (6.5)	100.9 (6.3)	99.8 (6.7)	102.0 (5.3)	98.6 (5.1)	100.3 (6.0)	
Median	101.0	99.0	100.5	100.0	103.0	98.0	100.0	
Range	91.0 to 115.0	79.0 to 112.0	83.0 to 117.0	79.0 to 115.0	90.0 to 111.0	87.0 to 110.0	79.0 to 117.0	

[a] From ANOVA with main effect treatment
[b] BMI is the baseline weight in kilograms divided by the square of the baseline height in meters
Cross Reference: Data Listings 10.1.1, 10.1.2, and 10.1.3
(Reproduced from Sponsor, Table 1.2.1, page 140)

In the ITT Population, common coexisting medical conditions in ≥ 5% of patients included hypercholesterolemia (15.0%), hysterectomy (15.0%), tubal ligation (9.7%), hyperlipidemia (8.0%), allergic rhinitis (7.3%), diabetes (6.0%), anemia (5.3%), GERD (5.3%), and sinusitis (5.3%).

In the ITT Population, 72.7% of patients used concomitant medication during the study. Medications used in ≥ 5.0% of patients included paracetamol/acetaminophen (9.3%), acetylsalicylic acid (8.3%), multivitamins (6.7%), atorvastatin (6.3%), conjugated estrogens (6.0%), and ibuprofen (6.0%). Medications which varied between treatment groups included atorvastatin (nebivolol 2.5 mg: 0 % vs. placebo: 10.2%), conjugated estrogens (nebivolol 2.5 mg: 0% vs. nebivolol 5 mg: 10.0%), ibuprofen (nebivolol 40 mg: 0% vs. placebo: 14.3%), multivitamins (nebivolol 20 mg: 2% vs. nebivolol 2.5 mg: 14.3%), and paracetamol (nebivolol 5 mg: 4.0% vs. nebivolol 5 mg: 14.0%).

Subject disposition is shown in Table 114 below. Patient 2463000720 was accidentally unblinded during the placebo run-in period and was discontinued from the study.

Table 114. Patient Disposition (ITT Population) (NEB-202)

End of Study Status Discontinuation Reason	Placebo n (%)	Nebivolol 2.5 mg n (%)	Nebivolol 5 mg n (%)	Nebivolol 10 mg n (%)	Nebivolol 20 mg n (%)	Nebivolol 40 mg n (%)	Total for All Nebivolol Patients n (%)	Total for All Patients n (%)
ITT	49	49	50	51	50	51	251	300
Completed								
Total	41 (83.7)	42 (85.7)	41 (82.0)	47 (92.2)	45 (90.0)	43 (84.3)	218 (86.9)	259 (86.3)
Discontinued								
Total	8 (16.3)	7 (14.3)	9 (18.0)	4 (7.8)	5 (10.0)	8 (15.7)	33 (13.1)	41 (13.7)
Adverse Event	0 (0.0)	1 (2.0)	2 (4.0)	0 (0.0)	1 (2.0)	2 (3.9)	6 (2.4)	6 (2.0)
Treatment Failure	4 (8.2)	1 (2.0)	2 (4.0)	0 (0.0)	1 (2.0)	2 (3.9)	6 (2.4)	10 (3.3)
Lost to Follow-up	1 (2.0)	2 (4.1)	3 (6.0)	1 (2.0)	0 (0.0)	2 (3.9)	8 (3.2)	9 (3.0)
Protocol Deviation	1 (2.0)	0 (0.0)	0 (0.0)	2 (3.9)	1 (2.0)	1 (2.0)	4 (1.6)	5 (1.7)
Withdrew Consent	1 (2.0)	2 (4.1)	1 (2.0)	0 (0.0)	0 (0/0)	1 (2.0)	4 (1.6)	5 (1.7)
Other	1 (2.0)	1 (2.0)	1 (2.0)	1 (2.0)	2 (4.0)	0 (0.0)	5 (2.0)	6 (2.0)

Data Source: Table 1.8.1 and Table 1.8.2
[a] **Patient 2613000841 (nebivolol 5 mg) had a serious adverse event (SAE) of seizures that was pretreatment-emergent; however, the patient withdrew during the double-blind treatment period (see Section 12.3.1.3.1).**

(Reproduced from Sponsor, Table 10.1-1, page 58)

The sponsor's analysis of non-compliance (outside ± 10% of randomized dose) gave rates of 13.3% in the placebo group and a range from 2.0% to 16.0% in the nebivolol treatment groups. The highest noncompliance rate was 16.0% in the nebivolol 20 mg treatment group. The p-value, using a Chi-Square Test was 0.090.

Primary Efficacy Endpoint (Sitting Diastolic Blood Pressure at Trough) (NEB-202)

For the primary efficacy endpoint, the sponsor's analysis found the linear contrasts for nebivolol 5, 10, 20, and 40 mg in the ITT LOCF Population were statistically significant using the step-down trend test. At Day 84, the ITT OC and PP LOCF results supported the ITT LOCF results, except nebivolol 2.5 mg was statistically significant in step-down trend testing in the PP LOCF Population. For the PP OC Population, only nebivolol 40 mg was borderline statistically significant ($p = 0.050$) at the end of the study.

For the ITT LOCF Population, the antihypertensive effect of nebivolol 2.5, 5, 10, and 20 mg was apparent at day 14.

In the step-up trend test for the ITT LOCF Population including nebivolol 40 mg, the nebivolol contrast ranging from placebo to 40 mg was significant at end of study ($p < 0.001$). In the step-up trend test for the ITT LOCF Population excluding nebivolol 40 mg, the nebivolol contrasts

ranging from placebo to nebivolol 20 mg as well as from nebivolol 2.5 mg to 20 mg were significant. The results of step-down and step-up trend testing are shown in Table 115 below.

Table 115. Step-Down Trend Test, Step-Up Trend Test, and LS Mean Change from Baseline to End of Study in Sitting Diastolic Blood Pressure at Trough (ITT LOCF) (NEB-202)

Treatment	N	Baseline Mean	Treatment Mean	Mean Change from Baseline (SD)	LS Mean Change from Baseline (SE)[a]	Step-Down Trend Test p-value[a,b]	Step-Up Trend Test p-value[a,c]	Step-Up Trend Test p-value[a,d]
Placebo	49	100.8	96.4	-4.4 (8.8)	-2.8 (2.1)		< 0.001	< 0.001
Nebivolol								
2.5 mg	49	99.5	92.8	-6.8 (7.9)	-5.7 (2.1)	0.084	0.092	0.047
5 mg	50	100.5	91.4	-9.1 (9.1)	-7.7 (2.1)	0.004	0.741*	0.487
10 mg	51	100.3	90.0	-10.3 (8.2)	-8.9 (2.0)	< 0.001	0.718*	0.986*
20 mg	50	101.5	90.9	-10.6 (8.8)	-8.9 (2.1)	< 0.001	0.735*	
40 mg	51	98.7	89.6	-9.1 (7.4)	-8.3 (2.0)	< 0.001		NA

Data Source: Table 2.1.1. NA: not applicable.
[a] From an ANCOVA with factor treatment and covariates baseline blood pressure, age group, gender, diabetes status, and metabolism rate
[b] Step-down testing scheme began with treatments placebo through nebivolol 40 mg and proceeded to step down until the trend tests contained only placebo and nebivolol 2.5 mg
[c] Step-up testing scheme began with treatments placebo through nebivolol 40 mg and proceeded to step-up until the trend test contained only nebivolol 20 mg and 40 mg
[d] Step-up testing scheme began with treatments placebo through nebivolol 20 mg and proceeded to step-up until the trend test contained only nebivolol 10 mg and 20 mg.
***P-values associated with higher doses are not applicable in the context of step-up trend testing due to the nonsignificant result at the lower dose.**

(Reproduced from Sponsor, Table 11.4.1.1-2, page 66)

Differences from Placebo in LS Mean Change from Baseline in Sitting DBP at Trough (NEB-202)

In the ITT LOCF Population, the difference from placebo in LS mean change from baseline to end of study for the primary efficacy endpoint was statistically significant for nebivolol 5, 10, 20, and 40 mg. The difference from placebo is shown in Table 116. The ITT OC and PP LOCF Population pairwise comparisons supported the ITT LOCF results, except nebivolol 2.5 mg was also significant at end of study in the PP LOCF Population.

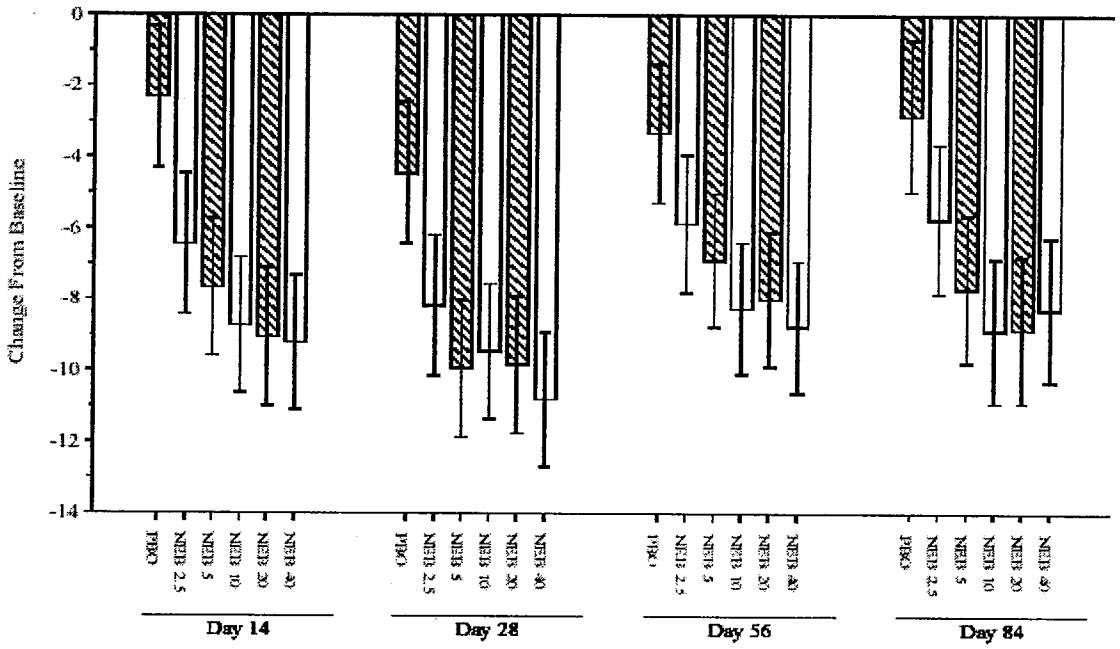
Table 116. Difference from Placebo in LS Mean Change From Baseline to End of Study in Sitting Diastolic Blood Pressure at Trough (ITT LOCF) (NEB-202)

Treatment	N	LS Mean Difference[a,b]	95% CI[a,b]	p-value[a,b]
Nebivolol				
2.5 mg	49	-2.9	(-6.2, 0.4)	0.084*
5 mg	50	-4.9	(-8.1, -1.6)	0.004
10 mg	51	-6.1	(-9.3, -2.8)	< 0.001
20 mg	50	-6.0	(-9.3, -2.8)	< 0.001
Nebivolol				
40 mg	51	-5.5	(-8.7, -2.2)	0.001

Data Source: Table 2.1.1
[a] **From an ANCOVA with factor treatment and covariates baseline blood pressure, age group, gender, diabetes status, and metabolism rate**
[b] **LS mean difference based on pairwise comparison of treatment vs. placebo**
* **P-value is not applicable due to non-significant results for this dose in step-down trend test**
(Reproduced from Sponsor, Table 11.4.1.1.1-1, page 68)

The sponsor's bar graph in Figure 19 illustrates the LS mean change in sitting DBP (trough) from baseline to end of study by visit for the ITT LOCF Population.

Figure 19. Bar Graph of LS Mean Change from Baseline to End of Study in Sitting DBP (mm Hg) at Trough by Treatment +/- SE (ITT LOCF Population) (NEB-202)



Data Source: Figure 1.1.2
(Reproduced from Sponsor, Figure 11.4.1.1.1-2, page 70)

There was no significant interaction by site regarding primary and secondary efficacy parameters. Peak standing diastolic blood pressure (mm Hg) trended towards significance in the ITT LOCF Population at Day 84 with p = 0.051.

Using the ITT Worst Case Carried Forward for the primary efficacy endpoint in the ITT LOCF Population, by step-down trend testing, nebivolol 5, 10, 20, and 40 mg were statistically significant ($p = 0.010$ for nebivolol 5 mg and $p < 0.001$ for nebivolol 10, 20, and 40 mg) at the end of study.

GCP Issues (NEB-202)

Bertek considered Site 325 to be a potential violator of GCP guidelines. After excluding this site, the sponsor found nebivolol 5 through 40 mg was statististically significant ($p \leq 0.017$) for the primary efficacy endpoint in the ITT LOCF Population at the end of treatment. By step-up trend testing, both the placebo through nebivolol 40 mg and 2.5 mg through 40 mg contrasts were statistically significant ($p \leq 0.010$).

Secondary Efficacy Endpoints (NEB-202)

Sitting Systolic Blood Pressure at Trough

For the ITT LOCF Population, by step-down trend testing for sitting SBP at trough from baseline to end of study, nebivolol 10, 20, and 40 mg were statistically significant ($p \leq .044$), as shown in Table 117 below. At the end of study, the ITT OC and PP LOCF analyses supported the ITT LOCF results, with the exception of nebivolol 10 mg in the ITT OC Population which was not statistically significant. No doses of nebivolol were significant in the PP OC Population at the end of study.

Table 117. Mean Change from Baseline to End of Study in Sitting Systolic Blood Pressure at Trough and Trend Tests (ITT LOCF) (NEB-202)

Treatment	N	Baseline Mean	Treatment Mean	Mean Change From Baseline (SD)	LS Mean Change from Baseline (SE)[a]	Step-Down Trend Test p-value[a,b]	Step-Up Trend Test p-value[a,c]	Step-Up Trend Test p-value[a,d]
Placebo	49	151.4	147.8	-3.6 (15.6)	-0.4 (3.8)		0.002	0.005
Nebivolol								
2.5 mg	49	148.6	144.0	-4.6 (15.5)	-1.9 (3.7)	0.611*	0.022	0.032
5 mg	50	151.7	145.8	-5.9 (17.8)	-3.0 (3.7)	0.383	0.133	0.118
10 mg	51	154.2	144.0	-10.2 (12.9)	-6.4 (3.6)	0.044	0.771*	0.668Ψ
20 mg	50	156.4	144.4	-12.0 (16.1)	-7.6 (3.7)	0.005	0.891*	
40 mg	51	150.9	141.4	-9.6 (14.4)	-7.2 (3.5)	0.002		NA

Data Source: Table 2.2.1. NA: not applicable.

[a] From an ANCOVA with factor treatment and covariates baseline blood pressure, age group, gender, diabetes status, and metabolism rate

[b] Step-down testing scheme began with treatments placebo through nebivolol 40 mg and proceeded to step down until the trend test contained only placebo and nebivolol 2.5 mg.

[c] Step-up testing scheme began with treatments placebo through nebivolol 40 mg and proceeded to step-up until the trend test contained only nebivolol 20 mg and 40 mg.

[d] Step-up testing scheme began with treatments placebo through nebivolol 20 mg and proceeded to step-up until the trend test contained only nebivolol 10 mg and 20 mg

*** P-values associated with lower doses are not applicable in the context of step-down trend testing due to the nonsignificant result at the higher dose.**

Ψ P-values associated with higher doses are not applicable in the context of step-up trend testing due to the non-significant result at the lower dose.

(Reproduced from Sponsor, Table 11.4.1.2.1.1-1, page 78)

For the ITT LOCF Population at end of study, step-up trend testing including nebivolol 40 mg was significant for the placebo through nebivolol 40 mg contrast. In step-up trend testing excluding nebivolol 40 mg, the placebo through nebivolol 40 mg as well as nebivolol 2.5 mg through 40 mg contrasts were significant.

In the ITT LOCF Population, pairwise differences from placebo in LS mean change from baseline in sitting SBP at trough to end of study was significant for nebivolol 10 mg through 40 mg ($p = 0.045$ for nebivolol 10 mg, $p = 0.016$ for nebivolol 20 mg, and $p = 0.022$ for nebivolol 40 mg).

Summary of Primary and Secondary Endpoints (NEB-202)

At trough, step-down trend testing in the ITT LOCF Population for change in sitting, standing, and supine diastolic blood pressure from baseline to end of study was significant for nebivolol 5 mg, 10 mg, 20 mg, and 40 mg. At peak, step-down trend testing for sitting, standing, and supine diastolic blood pressure was significant for nebivolol 5 mg through 40 mg. Additionally, at peak, sitting and supine diastolic blood pressure significantly responded to nebivolol 2.5 mg.

For systolic blood pressure at trough and peak, Table 118 summarizes the significant doses of nebivolol in the ITT LOCF Population at end of study:

Table 118. Significant Nebivolol Doses for SBP at Trough and Peak at End of Study (ITT LOCF) (NEB-202)

Blood Pressure Parameter	Nebivolol 2.5 mg	Nebivolol 5 mg	Nebivolol 10 mg	Nebivolol 20 mg	Nebivolol 40 mg
Trough					
Sitting SBP	NS	NS	X	X	X
Standing SBP	NS	NS	NS	NS	X
Supine SBP	NS	NS	NS	NS	NS
Peak					
Sitting SBP	NS	X	X	X	X
Standing SBP	NS	X	X	X	X
Supine SBP	NS	X	X	X	X
X = significant. NS = not significant.					

(Adapted from Sponsor, Tables 11.4.1.3-1 and 11.4.1.3-2, pages 93 and 94)

Table 119 and Table 120 summarize the step-down trend testing results for LS mean change in DBP and SBP at trough and peak from baseline to end of study.

Table 119. Summary of Results of the Step-Down Trend Test, LS Mean, and Difference From Placebo in LS Mean Change in Blood Pressure from Baseline to End of Study (Day 84) at Trough (ITT LOCF) (NEB-202)

Blood Pressure Parameter	Placebo	Nebivolol 2.5 mg			Nebivolol 5 mg			Nebivolol 10 mg			Nebivolol 20 mg			Nebivolol 40 mg		
	LS[c] Mean	p-value[a,b]	LS[c] Mean	LS Mean Diff[b,c]	p-value[a,b]	LS[c] Mean	LS Mean Diff[b,c]	p-value[a,b]	LS[c] Mean	LS Mean Diff[b,c]	p-value[a,b]	LS[c] Mean	LS Mean Diff[b,c]	p-value[a,b]	LS[c] Mean	LS Mean Diff[b,c]
Sitting																
DBP	-2.8	0.084	-5.7	-2.9	0.004	-7.7	-4.9	<0.001	-8.9	-6.1	<0.001	-8.9	-6.0	<0.001	-8.3	-5.5
SBP	-0.4	0.611*	-1.9	-1.5	0.383	-3.0	-2.6	0.044	-6.4	-6.0	0.005	-7.6	-7.3	0.002	-7.2	-6.8
Standing																
DBP	-5.1	0.651	-5.9	-0.8	0.044	-8.7	-3.6	0.003	-9.7	-4.6	0.002	-9.4	-4.3	<0.001	-10.1	-5.0
SBP	-4.0	>0.999*	-4.0	0.0	0.292*	-7.2	-3.2	0.175*	-7.2	-3.2	0.093	-8.1	-4.1	0.016	-10.2	-6.2
Supine																
DBP	-4.4	0.056	-7.8	-3.3	0.028	-8.2	-3.8	0.001	-10.1	-5.7	0.001	-9.6	-5.2	0.001	-9.5	-5.1
SBP	-5.4	0.943*	-5.1	0.2	0.965*	-5.5	-0.1	0.142*	-9.6	-4.3	0.175*	-7.4	-2.1	0.054	-9.6	-4.3

Data Source: Table 2.1.1, Table 2.2.1, Table 2.5.1, Table 2.6.1, Table 2.9.1, Table 2.10.1

[a] P-value from step-down trend test. Step-down testing began with placebo to nebivolol 40 mg and proceeded to step down until the test contained only placebo and nebivolol 2.5 mg.

[b] From an ANCOVA with factor treatment and covariates baseline blood pressure, age group, gender, diabetes status, and metabolism rate

[c] LS mean change in DBP or SBP from baseline to end of study; difference from placebo in LS mean change in DBP or SBP from baseline to end of study

***: P-values associated with lower doses are not applicable in the context of step-down trend testing due to the non-significant result at the higher dose.**

Note: P-value and LS mean difference are not applicable for placebo; therefore, these columns are not displayed.

(Reproduced from Sponsor, Table 11.4.1.3-1, page 93)

Table 120. Summary of Results of the Step-Down Trend Test, LS Mean, and Difference from Placebo in LS Mean Change in Blood Pressure from Baseline to End of Study (Day 84) at Peak (ITT LOCF) (NEB-202)

Blood Pressure Parameter	Placebo	Nebivolol 2.5 mg			Nebivolol 5 mg			Nebivolol 10 mg			Nebivolol 20 mg			Nebivolol 40 mg		
	LS[c] Mean	p-value[a,b]	LS[c] Mean	LS Mean Diff[b,c]	p-value[a,b]	LS[c] Mean	LS Mean Diff[b,c]	p-value[a,b]	LS[c] Mean	LS Mean Diff[b,c]	p-value[a,b]	LS[c] Mean	LS Mean Diff[b,c]	p-value[a,b]	LS[c] Mean	LS Mean Diff[b,c]
Sitting																
DBP	-3.8	0.008	-8.6	-4.8	<0.001	-10.6	-6.8	<0.001	-12.3	-8.5	<0.001	-10.9	-7.1	<0.001	-11.4	-7.6
SBP	-3.0	0.108	-7.8	-4.8	0.011	-10.6	-7.6	0.003	-11.4	-8.5	0.001	-12.1	-9.2	<0.001	-12.2	-9.2
Standing																
DBP	-4.6	0.122	-7.6	-3.0	0.001	-10.7	-6.1	<0.001	-11.5	-6.9	<0.001	-10.0	-5.4	<0.001	-10.5	-5.9
SBP	-3.9	0.208	-7.9	-4.0	0.007	-12.4	-8.5	0.006	-11.5	-7.5	0.009	-11.4	-7.5	0.010	-11.6	-7.7
Supine																
DBP	-5.5	0.022	-9.8	-4.3	0.005	-10.7	-5.3	<0.001	-11.9	-6.5	<0.001	-11.8	-6.3	<0.001	-11.8	-6.3
SBP	-4.9	0.138	-9.5	-4.6	0.028	-11.7	-6.8	0.004	-13.6	-8.7	0.002	-13.6	-8.7	0.002	-13.4	-8.5

Data Source: Table 2.3.1, Table 2.4.1, Table 2.7.1, Table 2.8.1, Table 2.11.1, Table 2.12.1

[a] P-value from step-down trend test. Step-down testing began with placebo to nebivolol 40 mg and proceeded to step down until the test contained only placebo and nebivolol 2.5 mg.

[b] From an ANCOVA with factor treatment and covariates baseline blood pressure, age group, gender, diabetes status, and metabolism rate

[c] LS mean change in DBP or SBP from baseline to end of study; difference from placebo in LS mean change in DBP or SBP from baseline to end of study

***: P-values associated with lower doses are not applicable in the context of step-down trend testing due to the non-significant result at the higher dose.**

Note: P-value and LS mean difference are not applicable for placebo; therefore, these columns are not displayed.

(Reproduced from Sponsor, Table 11.4.1.3-2, page 94)

Subgroup Analyses (NEB-202)

Change in Sitting DBP at Trough by Subgroup

The sponsor performed subgroup analyses (age, gender, BMI, and diabetes status) on the primary endpoint, change in diastolic blood pressure at trough from baseline to end of study. For most of these subgroups, there was an unequal distribution of these patients in treatment groups and an inadequate sample size, so no definitive conclusions can be made. In general, nebivolol decreased sitting DBP over placebo, although there were some exceptions with nebivolol 2.5 mg. The subgroup analyses are summarized in Table 121 and Table 122.

Table 121. Summary of Change in Sitting DBP from Baseline to End of Study by Subgroup (Age and Gender; ITT LOCF) (NEB-202)

	Age						Gender					
	<65			≥65			Male			Female		
	N	LS Mean[a,b] (SE)	LS Mean Diff[b,c]	N	LS Mean[a,b] (SE)	LS Mean Diff[b,c]	N	LS Mean[a,b] (SE)	LS Mean Diff[b,c]	N	LS Mean[a,b] (SE)	LS Mean Diff[b,c]
Placebo	44	-4.0 (2.3)	—	5	1.9 (6.7)	—	23	-1.7 (2.8)	—	26	-1.1 (3.7)	—
Nebivolol												
2.5mg	45	-6.7 (2.3)	-2.7	4	3.5 (6.7)	1.5	26	-7.8 (2.7)	-6.1	23	-1.1 (3.8)	0.1
5mg	44	-7.8 (2.2)	-3.7	6	-9.8 (6.2)	-11.7	22	-10.9 (2.7)	-9.2	28	-2.4 (3.6)	-1.2
10mg	45	-8.8 (2.2)	-4.8	6	-13.0 (6.8)	-14.9	22	-9.1 (2.7)	-7.4	29	-6.2 (3.5)	-5.1
20mg	45	-9.3 (2.3)	-5.3	5	-8.1 (5.0)	-10.1	21	-9.7 (2.7)	-8.0	29	-5.6 (3.6)	-4.4
40mg	42	-9.0 (2.3)	-5.0	9	-8.9 (5.4)	-10.8	22	-9.0 (2.7)	-7.4	29	-5.4 (3.4)	-4.2

Data Source: Table 11.2
[a]LS mean change in DBP from baseline to end of study
[b]From an ANCOVA with factor treatment and covariates baseline blood pressure, age group, gender, diabetes status, and EM or PM classification with covariate from the analysis removed from the model
[c]Based on pairwise comparison of treatment vs. placebo

(Reproduced from Sponsor, Table 11.4.2.8.1-1, page 98)

Table 122. Summary of Change in Sitting DBP from Baseline to End of Study by Subgroup (BMI and Diabetes Status; ITT LOCF) (NEB-202)

	BMI						Diabetes Status					
	BMI (kg/m2) <30			BMI (kg/m2) ≥30			Yes			No		
	N	LS Mean[a,b] (SE)	LS Mean Diff[b,c]	N	LS Mean[a,b] (SE)	LS Mean Diff[b,c]	N	LS Mean[a,b] (SE)	LS Mean Diff[b,c]	N	LS Mean[a,b] (SE)	LS Mean Diff[b,c]
Placebo	21	-2.1 (3.7)	—	28	-4.4 (2.6)	—	6	-2.2 (3.4)	—	43	-4.3 (2.2)	—
Nebivolol												
2.5mg	20	-8.3 (3.7)	-6.2	23	-4.4 (2.6)	0.0	7	-7.1 (2.9)	-4.9	42	-6.7 (2.1)	-2.3
5mg	26	-8.5 (3.6)	-6.3	24	-8.2 (2.6)	-3.8	8	-3.3 (2.8)	-1.1	42	-9.8 (2.1)	-5.5
10mg	26	-8.9 (3.5)	-5.8	25	-10.9 (2.5)	-6.5	6	-6.6 (3.4)	-4.3	45	-10.5 (2.0)	-6.1
20mg	25	-12.5 (3.6)	-10.3	25	-6.2 (2.6)	-1.8	7	-11.4 (2.8)	-9.2	43	-9.5 (2.1)	-5.2
40mg	20	-9.0 (3.5)	-6.9	31	-8.7 (2.5)	-4.3	9	-9.9 (2.8)	-7.7	42	-9.4 (2.1)	-5.1

Data Source: Table 11.2
[a]LS mean change in DBP from baseline to end of study
[b]From an ANCOVA with factor treatment and covariates baseline blood pressure, age group, gender, diabetes status, and EM or PM classification with covariate from the analysis removed from the model
[c]Based on pairwise comparison of treatment vs. placebo

(Reproduced from Sponsor; Table 11.4.2.8.1-2, page 99)

Response Rates (NEB-202)

The definition of a responder for Study NEB-202 was the same as for Studies NEB-302 and NEB-305. In the ITT LOCF Population, there were significantly more responders compared to placebo for nebivolol 5 mg through 40 mg treatment groups as shown in Table 123.

Table 123. Responder Rates[a] by Treatment. Evaluation of Possible Predictors of Responders. (ITT LOCF) (NEB-202)

Treatment	Total	Responder n (%)[b]	p-value[c]
Placebo	49	13 (26.5)	
Nebivolol 2.5 mg	49	18 (36.7)	0.287
Nebivolol 5 mg	50	29 (58.0)	0.002
Nebivolol 10 mg	51	30 (58.8)	< 0.001
Nebivolol 20 mg	50	32 (64.0)	< 0.001
Nebivolol 40 mg	51	29 (56.9)	< 0.001

[a] A subject is a responder if their average trough sitting diastolic blood pressure < 90 mm Hg at end of study or has decreased by ≥ 10 mm Hg from baseline
[b] Percentage is the percentage of responders within that category
[c] Based on Wald Chi-Square Test for trend from logistic regression with factor treatment and covariates baseline blood pressure, EM or PM classification, diabetes status, gender, and age group; Step-down testing scheme begins with treatments placebo through Nebivolol 40 mg and proceeds to step-down until the trend test contains only placebo and nebivolol 2.5 mg
NS: P-values should not be used in the context of step-down trend testing (see analysis plan for explanation)
Cross Reference: Data Listings 1, 10.1.1, 10.2.1, 10.4, and 14.3

(Reproduced from Sponsor, Table 2.13.1, page 480)

Most nebivolol patients responded by Day 14, although in the nebivolol 20 mg treatment group, the greatest response was evident by Day 56, as shown in Table 124 below.

Table 124. Responder[a] Rates by Treatment and Visit (Population: Intent-to-Treat Last Observation Carried Forward) (Study NEB-202)

Visit	Placebo	Nebivolol 2.5 mg n (%)	Nebivolol 5 mg n (%)	Nebivolol 10 mg n (%)	Nebivolol 20 mg n (%)	Nebivolol 40 mg n (%)	Total n (%)
Day 14	11 (22.4)	21 (42.9)	24 (48.0)	25 (49.0)	26 (52.0)	30 (58.8)	137 (45.7)
Day 28	11 (22.4)	23 (46.9)	25 (50.0)	23 (45.1)	29 (58.0)	31 (60.8)	142 (47.3)
Day 56	16 (32.7)	23 (46.9)	24 (48.0)	24 (47.1)	32 (64.0)	30 (58.8)	149 (49.7)
Day 84	13 (26.5)	18 (36.7)	29 (58.0)	30 (58.8)	32 (64.0)	29 (56.9)	151 (50.3)

[a] A subject is a responder if their average trough sitting diastolic blood pressure < 90 mm Hg at endpoint of interest or has decreased by ≥ 10 mm hg from baseline
[b] Percentage is the percentage of responders within that category
Cross Reference: Data Listings 10.1.1, 10.2.1, and 10.4

(Reproduced from Sponsor, Table 2.13.5, page 484)

Response Rate by Subgroup (NEB-202)

The small number of patients in all of the subgroups and the placebo population make these results difficult to interpret. Overall, however, non diabetics had significantly better response rates than diabetics (p = 0.040), as seen in Table 125.

Table 125. Responder[a] Rates by Treatment and Baseline Characteristics at Day 84 (End of Study) (ITT LOCF) (NEB-202)

Characteristic Subgroup	Placebo n (%)[b]	Nebivolol 2.5 mg n (%)[b]	Nebivolol 5 mg n (%)[b]	Nebivolol 10 mg n (%)[b]	Nebivolol 20 mg n (%)[b]	Nebivolol 40 mg n (%)b	Total N (%)[b]	Subgroup p-value[c]
Age								
< 65	12 (27.3)	16 (35.6)	26 (59.1)	26 (57.8)	28 (62.2)	25 (59.5)	133 (50.2)	0.915
≥ 65	1 (20.0)	2 (50.0)	3 (50.0)	4 (66.7)	4 (80.0)	4 (44.4)	18 (51.4)	
Gender								
Male	4 (17.4)	10 (38.5)	15 (68.2)	12 (54.5)	14 (66.7)	10 (45.5)	65 (47.8%)	0.739
Female	9 (34.6)	8 (34.8)	14 (50.0)	18 (62.1)	18 (62.1)	19 (65.5)	86 (52.4)	
Diabetes Status								
Yes	0 (0.0)	2 (28.6)	3 (37.5)	2 (33.3)	4 (57.1)	5 (55.6)	16 (37.2)	**0.040**
No	13 (0.2)	16 (38.1)	26 (61.9)	28 (62.2)	28 (65.1)	24 (57.1)	135 (52.5)	
EM or PM Classification								
Poor	0 (0.0)	1 (100.0)	1 (100.0)	1 (50.0)	1 (100.0)	0 (0.0)	4 (57.1)	0.923
Extensive	13 (26.5)	17 (35.4)	28 (57.1)	29 (59.2)	31 (63.3)	29 (59.2)	147 (50.2)	

[a] A subject is a responder if their average trough sitting diastolic blood pressure < 90 mm Hg at end of study or has decreased by ≥ 10 mm Hg from baseline
[b] Percentage is the percentage of responders within that category
[c] Test of difference between subgroups based on Wald Chi-Square Test from logistic regression with factor treatment and covariates
baseline blood pressure, EM or PM classification, diabetes status, gender, and age group
Cross Reference: Data Listings 1, 10.1.1, 10.2.1, 10.4, and 14.3
(Reproduced from Sponsor, Table 2.13.9, page 488)

Trough to Peak Ratios (NEB-202)

The placebo subtracted trough-to-peak ratios for change in sitting DBP from baseline to end of study are shown in Table 126 below.

Table 126. Placebo Subtracted Trough to Peak Ratio for Change from Baseline in Sitting Diastolic Blood Pressure at Day 84 (ITT LOCF) (Study NEB-202)

Treatment	Trough Mean	Peak Mean	Active - Placebo		
			Trough Mean	Peak Mean	Ratio
Placebo	-4.4	-5.7			NA
Nebivolol 2.5 mg	-6.8	-9.6	-2.3	-3.9	0.6
Nebivolol 5 mg	-9.1	-12.2	-4.7	-6.5	0.7
Nebivolol 10 mg	-10.3	-13.9	-5.8	-8.2	0.7
Nebivolol 20 mg	-10.6	-13.0	-6.2	-7.3	0.8
Nebivolol 40 mg	-9.1	-12.2	-4.6	-6.5	0.7
Cross Reference: Data Listings 10.1.1, 10.2.1, 10.3.1, and 10.4					

(Reproduced from Sponsor, Table 11.1, page 502)

Duration of Study Medication Exposure

The duration of study medication exposure in days is described in Table 127. According to the sponsor on page 103, "a total of 176 (70.1%) nebivolol-treated patients and 30 (61.2%) placebo-treated patients took at least 84 days of study drug."

Table 127. Duration[a] of Study Medication (days) (Population: Intent-to-Treat) (Study NEB-202)

Duration	Placebo n (%)	Nebivolol 2.5 mg n (%)	Nebivolol 5 mg n (%)	Nebivolol 10 mg n (%)	Nebivolol 20 mg n (%)	Nebivolol 40 mg n (%)	Total Nebivolol n (%)	Total n (%)	p-value[a]
N	49	49	50	51	50	51	251	300	0.697
Mean (SD)	75.2 (22.7)	77.5 (19.2)	77.8 (20.8)	80.9 (16.8)	80.6 (14.9)	77.9 (20.1)	78.9 (18.4)	78.3 (19.2)	
Median	85.0	85.0	85.0	85.0	85.0	85.0	85.0	85.0	
Range	1.0 to 89.0	18.0 to 89.0	1.0 to 89.0	1.0 to 89.0	12.0 to 89.0	1.0 to 89.0	1.0 to 89.0	1.0 to 89.0	
0-14 Days	2 (4.1)	0 (0.0)	2 (4.0)	2 (3.9)	1 (2.0)	1 (2.0)	6 (2.4)	8 (2.7)	
15-28 Days	1 (2.0)	2 (4.1)	2 (4.0)	0 (0.0)	0 (0.0)	1 (2.0)	5 (2.0)	6 (2.0)	
29-56 Days	6 (12.2)	5 (10.2)	1 (2.0)	1 (2.0)	3 (6.0)	4 (7.8)	14 (5.6)	20 (6.7)	
57-84 Days	5 (10.2)	8 (16.3)	7 (14.0)	5 (9.8)	10 (20.0)	5 (9.8)	35 (13.9)	40 (13.3)	
≥ 84 Days	35 (71.4)	34 (69.4)	38 (76.0)	43 (84.3)	36 (72.0)	40 (78.4)	191 (76.1)	226 (75.3)	

[a] **If the date of last dose is missing, the date of last visit will be used in the calculation for duration of study medication. If the treatment duration exceeds 89 days, then 89 days will be used in the analysis.**
[b] **From ANOVA with main effect treatment**
Cross Reference: Data Listings 9

(Reproduced from Sponsor, Table 1.9, page 284)

Overall, 301 patients were randomized, 1 patient did not take study drug and was defined as the "non-ITT Population," and 259/300 (86.3%) completed Study NEB-202. Nine patients (3%) were lost to follow-up. There were no deaths. According to the sponsor's analysis, major protocol deviations are described in Table 128.

Table 128. Major Protocol Violations (Study NEB-202)

Criteria Violated	Placebo	Nebivolol 2.5 mg n (%)	Nebivolol 5 mg n (%)	Nebivolol 10 mg n (%)	Nebivolol 20 mg n (%)	Nebivolol 40 mg n (%)	Total Nebivolol n (%)	Total n (%)
DBP < 95 mm Hg at Baseline	0 (0.0)	2 (4.1)	1 (2.0)	2 (3.9)	1 (2.0)	4 (7.8)	10 (4.0)	10 (3.3)
DBP > 109 mm Hg at Baseline	1 (2.0)	0 (0.0)	0 (0.0)	1 (2.0)	2 (4.0)	0 (0.0)	3 (1.2)	4 (1.3)
Concomitant Antihypertensive Usage	2 (4.1)	0 (0.0)	3 (6.0)	1 (2.0)	3 (6.0)	3 (5.9)	10 (4.0)	12 (4.0)
Last Clinic Visit Trough Measurement < 22 or > 28 hours post previous dose	7 (14.3)	6 (12.2)	6 (12.0)	1 (2.0)	4 (8.0)	1 (2.0)	18 (7.2)	25 (8.3)

Criteria Violated	Placebo	Nebivolol 2.5 mg n (%)	Nebivolol 5 mg n (%)	Nebivolol 10 mg n (%)	Nebivolol 20 mg n (%)	Nebivolol 40 mg n (%)	Total Nebivolol n (%)	Total n (%)
Last Clinic Visit Peak Measurement < 2 or > 3 hours post previous dose	7 (14.3)	8 (16.3)	14 (28.0)	6 (11.8)	8 (16.0)	8 (15.7)	44 (17.5%)	51 (17.0)
Clinic Visit > 3 days off from scheduled visit	11 (22.4)	11 (22.4)	13 (26.0)	14 (27.5)	16 (32.0)	15 (29.4)	69 (27.5)	80 (26.7)
Baseline Sitting DBP at Trough > 2 days before first dose	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (0.4)	1 (0.3)
Received Incorrect Treatment (incorrect bottle codes)	4 (8.2)	3 (6.1)	4 (8.0)	7 (13.7)	0 (0.0)	4 (7.8)	18 (7.2)	22 (7.3)

[a] Includes all exclusionary medications with a stop date of less than or equal to 14 days of date of first double blind dose.
Cross Reference: Data Listing 16

(Adapted from Sponsor, Table 1.11, pages 286-287)

Summary

For the primary endpoint, sitting diastolic blood pressure at trough from baseline to end of study, nebivolol 5 mg, 10 mg, 20 mg, and 40 mg were statistically significant in step-down trend testing in the ITT LOCF Population.

In the step-up trend test for the primary endpoint in the ITT LOCF Population, the nebivolol contrast ranging from placebo to 40 mg as well as the placebo to nebivolol 20 mg and nebivolol 2.5 to 20 mg contrasts were statistically significant.

For standing and supine diastolic blood pressure at trough, nebivolol 5 mg through 40 mg was statistically significant in step-down trend testing. At peak, sitting, standing, and supine diastolic blood pressures were significantly reduced by nebivolol 5 mg through 40 mg. Additionally, sitting and supine diastolic blood pressure at peak was also significantly reduced by nebivolol 2.5 mg.

For change in sitting systolic blood pressure at trough from baseline to end of study, nebivolol 10 mg, 20 mg, and 40 mg was significant. For standing systolic blood pressure, only nebivolol 40 mg was significant. For supine systolic blood pressure, there were no significant nebivolol doses.

For change in sitting, standing, and supine systolic blood pressure at peak from baseline to end of study, nebivolol 5 mg through 40 mg was statistically significant.

In Study NEB-202, the trough to peak ratios for sitting diastolic blood pressure from baseline to end of study were only ≥0.7 for nebivolol 5 mg through 40 mg, which was different from Study NEB-302 (overall ratio of 0.9 for nebivolol 1.25 mg through nebivolol 30/40 mg) and Study NEB-305 (ratio of ≥ 0.8 for nebivolol 5mg through 20 mg).

11.4 NEB-203 (Pivotal) ("A Double-Blind, Randomized, Multi-Center, Active Comparator, Five Treatment Study of the Effects of Nebivolol Compared to Atenolol on Cardiovascular Hemodynamics and Exercise Capacity in Patients with Mild to Moderate Hypertension (Dose Finding Exercise and Mechanistic Study in Hypertension)")

Investigators

The 28 Investigators are listed in Table 129 below. All 28 sites were in the US. Individual sites (n = 17) randomized between 0 and 15 patients.

Table 129. Investigators (Study NEB-203)

Investigator	Site	# Pts	Investigator	Site	# Pts
		3			8
		0			0
		4			5
		3			13
		5			0
		11			0
		15			10
		0			4
		1			10
		0			0
		0			0
		14			2
		0			3
		0			4

Study Dates

May 29, 2002 – August 13, 2003

Study Design

This study description was based upon the protocol dated December 11, 2001 and an administrative change dated January 1, 2002. This was a Pilot, Phase II double blind, randomized, multicenter, active-comparator, five treatment parallel group dose finding and mechanistic study in patients with mild to moderate hypertension. The sponsor used this Pilot study to evaluate data collection methodology and dosing options for subsequent Phase III studies. The sponsor did not power NEB-203 to determine superiority of one treatment group over another, even between nebivolol groups. The primary focus of this study was to record preliminary data on exercise tolerance. Study NEB-203 had two phases. Phase I consisted of screening, followed by washout/single-blind placebo run in (up to 42 days). Phase II consisted of randomization and double-blind treatment for 28 days. Patients were randomized to atenolol 50 mg, atenolol 100 mg, nebivolol 5 mg, nebivolol 10 mg, or nebivolol 20 mg. NEB-203 stratified patients in all treatment groups by metabolism of nebivolol (poor vs. extensive

metabolizer), history of diabetes, race, age, and gender. There were five study visits on days 0 to -42, days -14 to -1, day 0, day 14, and day 28. The goal was to enroll 110 patients and to randomize them into 5 parallel groups.

Baseline assessments included history, physical examination, 12-lead ECG, beta-HCG urine pregnancy test (for women), routine laboratory evaluation, and genomics testing for cytochrome P450-2D6 analysis. Investigators performed pharmacokinetic sampling on Day 28.

Study drug was to be taken between 7 AM and 10 AM each day with or without breakfast. On clinic days, study drug administration was deferred until the investigator obtained trough blood pressure and heart rate measurements. The investigator measured trough vital signs during all 5 clinic visits and peak vital signs during Visit 3 (Day 0) and Visit 5 (Day 28), or sooner, if the investigator discontinued the patient from the study.

During Visit 2, from days -14 to -1, patients underwent one maximal exercise treadmill test (ETT), an echo-doppler study, and two sub-maximal ETTs. From Day -7 to Day -1, patients underwent a third submaximal treadmill test if required.[32] During Visit 5 on Day 18, patients underwent an echo-doppler study performed at trough plasma level, sub-maximal ETT performed at peak plasma level, and nebivolol assay, measured after completion of the last sub-maximal exercise test. Trough plasma level was considered to be 24 ± 2 hours post the previous morning's dose and two hours following the final dose of study medication. Peak plasma level was approximately 2-3 hours after the final dose of study medication. To estimate the plasma concentration for *d,l*-nebivolol, the sponsor added individual plasma concentrations of *d*-nebivolol and *l*-nebivolol.

Two different types of cycle ergometers were used during NEB-203 for maximal and submaximal ETTs. Initially, sites received the [redacted] which required manual calibration. Because there were issues with reproducibility, the [redacted] ergometer was replaced [redacted] which was automatically calibrated. Sites continued to use the [redacted] ergometer in patients who had already performed baseline maximal and submaximal ETTs on this ergometer but used the [redacted] model in newly enrolled patients. With the introduction of the [redacted] ergometer, the revised case report form allowed exercise time to be recorded in minutes and seconds, compared with minutes alone in the initial case report form.

The sponsor defined a responder as a subject whose average trough sitting diastolic blood pressure was less than 90 mm Hg or had decreased by at least 10 mm Hg from baseline at the end of study.

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32 **If the difference in exercise duration between sub-maximal ETT #1 and #2 was < 15%, then the results from sub-maximal ETT #2 were used as the baseline. If the difference between sub-maximal ETTs #1 and #2 was ≥ 15%, then the patient underwent sub-maximal ETT #3 within 7 days of sub-maximal ETT #2, and the results were used as the baseline.**

Inclusion Criteria for Study NEB-203 (Reproduced from Sponsor, page 33)

- Signed informed consent
- Males or Females[33] age ≥ 18 years
- High probability for compliance and study completion
- Ability to perform sustained dynamic exercise on a cycle ergometer
- Ambulatory blood pressures as follows
  - At screening Visit 1, an average sitting DBP of ≥ 95 mm Hg and ≤ 109 mm Hg if not currently receiving antihypertensive treatment
  - At screening Visit 1, an average sitting DBP of ≥ 80 mm Hg and ≤ 109 mm Hg if currently receiving antihypertensive treatment
  - At screening Visit 1, patients currently receiving antihypertensive treatment with an average sitting DBP < 80 mm Hg were permitted to continue the screening process only if the AE profile of their current antihypertensive medication(s) warranted a change in drug treatment
  - At randomization, Visit 3, an average sitting DBP ≥ 95 mm Hg and ≤ 109 mm Hg.

Exclusion criteria, prohibited medication, and restricted medications were identical to those in NEB-302. For NSAIDs in NEB-203, however, use could not exceed 2 consecutive days, compared with 5 days for NEB-302. Additionally, SSRIs in NEB-203 were prohibited unless the patient was on a stable dose for at least 2 months prior to Visit 1, compared with 3 months for NEB-302.

In patients with mild to moderate hypertension, the sponsor had four study objectives, as stated on page 28:

- determine the dose response effects of exercise capacity (duration of sub-maximal exercise at 75% of maximal workload) of nebivolol compared to atenolol in patients with mild to moderate hypertension
- determine the antihypertensive dose response effects of nebivolol compared to atenolol in patients with mild to moderate hypertension
- determine the dose response effects on left ventricular systolic and diastolic performance of nebivolol compared to atenolol in patients with mild to moderate hypertension
- evaluate data collection methodology and dosing options for a potential Phase III exercise study

The primary endpoint was the percent change in sub-maximal exercise duration by cycle ergometer at peak at end of treatment compared with baseline.

The primary analysis was ITT OC, because peak submaximal exercise duration had only one scheduled post-baseline measurement. ITT LOCF was a secondary method of data analysis. For the PP population, OC and LOCF were the primary and secondary methods of data handling, respectively. Another deviation from the protocol-defined statistical plan included the elimination of the recording of systolic blood pressure and heart rate at end of study, because

[33] **Women could not be pregnant or nursing. Women of childbearing potential were required to use appropriate contraception to participate in this study.**

most patients could not exercise for the prespecified 12 minutes on the sub-maximal ETT. The sponsor conducted the primary efficacy analysis using an analysis of covariance (ANCOVA) model with treatment as factor and metabolism of nebivolol (poor vs. extensive metabolizer), history of diabetes, race, age, and gender as covariates.

As stated by the sponsor on page 7 of NEB-203, the secondary efficacy variables included

- the change in sub-maximal exercise duration by cycle ergometer at peak at end of treatment compared to baseline
- the percent change and change in sub-maximal exercise systolic blood pressure (SBP) and heart rate at the end of the treatment compared to baseline
- the percent change and change in sitting and standing heart rate taken at peak (2-3 hours post-dose) and trough (24 ± 2 hours post previous morning's dose) at end of treatment compared to baseline
- the percent change and change in the mean sitting, standing, and supine SBP and diastolic blood pressure (DBP) at trough (24 ± 2 hours post previous morning's dose) and peak (2 to 3 hours post-dose) at end of treatment compared to baseline
- the response rate of treatment groups
- assessment of left ventricular (LV) systolic and diastolic performance using imaging and Doppler echocardiographic measurements at end of treatment compared to baseline
- generalized fatigue as measured by a fatigue severity scale at end of treatment compared to baseline
- evaluation of final Rating of Perceived Exertion (RPE) during the sub-maximal ETT at end of treatment compared to baseline
- correlation of peak plasma levels with change from baseline in sitting DBP and heart rate at end of treatment

Investigators reported serious adverse events [redacted] within 24 hours.

Results (NEB-203)
Because 38% (8/21) of patients in the atenolol 100 mg group did not perform the final sub-maximal ETT, compared with 4% (1/24) of atenolol 50 mg, 4% (1/23) of nebivolol 5 mg, 9% (2/23) of nebivolol 10 mg, and 0% of nebivolol 20 mg patients, interpretation of ITT OC data for NEB-203 is limited.

The demographic and baseline characteristics for the ITT population in NEB-203 are shown in Table 130.

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Table 130. Baseline Patient Characteristics by Treatment (ITT) (NEB-203)

Parameter	Atenolol 50 mg n (%)	Atenolol 100 mg n (%)	Nebivolol 5 mg n (%)	Nebivolol 10 mg n (%)	Nebivolol 20 mg n (%)	Total N (%)	p-value[a]
Age (years)							
N	24	21	23	23	24	115	0.841
Mean (SD)	51.1 (13.8)	51.8 (11.1)	48.2 (9.0)	51.3 (11.9)	51.0 (9.7)	50.7 (11.1)	
Median	51.0	51.0	49.0	50.0	52.5	50.0	
Range	(29.0, 79.0)	(34.0, 74.0)	(33.0, 72.0)	(21.0, 76.0)	(35.0, 69.0)	(21.0, 79.0)	
Age Group							
< 65	19 (79.2)	17 (81.0)	22 (95.7)	21 (91.3)	22 (91.7)	101 (87.8)	0.340
≥ 65	5 (20.8)	4 (19.0)	1 (4.3)	2 (8.7)	2 (8.3)	14 (12.2)	
Gender							
Male	17 (70.8)	16 (76.2)	18 (78.3)	17 (73.9)	17 (70.8)	85 (73.9)	0.972
Female	7 (29.2)	5 (23.8)	5 (21.7)	6 (26.1)	7 (29.2)	30 (26.1)	
Race[b]							
Black	4 (16.7)	2 (9.5)	4 (17.4)	4 (17.4)	3 (12.5)	17 (14.8)	0.928
Non-Black	20 (83.3)	19 (90.5)	19 (82.6)	19 (82.6)	21 (87.5)	98 (85.2)	
Caucasian	17 (70.8)	16 (76.2)	19 (82.6)	19 (82.6)	19 (79.2)	90 (78.3)	
Asian	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	
Hispanic	1 (4.2)	1 (4.8)	0 (0.0)	0 (0.0)	1 (4.2)	3 (2.6)	
Other	1 (4.2)	2 (9.5)	0 (0.0)	0 (0.0)	1 (4.2)	4 (3.5)	
Diabetes Status							
Yes	2 (8.3)	1 (4.8)	1 (4.3)	1 (4.3)	2 (8.3)	7 (6.1)	0.947
No	22 (91.7)	20 (95.2)	22 (95.7)	22 (95.7)	22 (91.7)	108 (93.9)	
EM or PM Classification							
Poor	1 (4.2)	1 (4.8)	1 (4.3)	1 (4.3)	1 (4.2)	5 (4.3)	>0.999
Extensive	23 (95.8)	20 (95.2)	22 (95.7)	22 (95.7)	23 (95.8)	110 (95.7)	
BMI[c] (kg/m^2)							
< 30	15 (62.5)	13 (61.9)	14 (60.9)	14 (60.9)	15 (62.5)	71 (61.7)	>0.999
≥ 30	9 (37.5)	8 (38.1)	9 (39.1)	9 (39.1)	9 (37.5)	44 (38.3)	

[a] **From ANOVA with main effect treatment for continuous variables; From a Chi-Square Test for discrete variables**
[b] **Test of race is black vs. non-black**
[c] **BMI is the baseline weight in kilograms divided by the square of the baseline height in meters**
Cross Reference Data Listings 1 and 16.3

(Reproduced from Sponsor, NEB-203, Table 1.1.1, pages 145 and 146)

Common co-existing conditions in over 5% of patients were hypercholesterolemia, hyperlipidemia, seasonal allergies, anxiety, depression, chronic sinusitis, and osteoarthritis.

There was no significant difference in medication compliance between treatment groups. Compliance was 83.3% and 73.7% in atenolol 50 mg and 100 mg treatment groups, respectively. In the nebivolol treatment groups, compliance ranged from 87% to 95.8%.

Patient disposition for NEB-203 is described in Table 131.